IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

MERCK SHARP & DOHME PHARMACEUTICALS, SRL, Plaintiff, v. TEVA PHARMACEUTICALS USA, INC., and TEVA PHARMACEUTICAL INDUSTRIES, LTD. Defendants.	C.A. No. 07-1596 (GEB) (JJH)

MERCK SHARP & DOHME PHARMACEUTICALS, SRL'S
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MERCK'S PROPOSED FINDINGS OF FACT

I. Introduction

A. The Parties

1. Plaintiff Merck Sharpe & Dohme Pharmaceuticals, SRL ("MSD") is a restricted liability society organized under the laws of Barbados, with offices at Chancery House, High Street, Bridgetown, Barbados. [Revised Final Pretrial Order, Stipulated Fact 1.]

2. Defendant Teva Pharmaceuticals USA, Inc. ("Teva" shall collectively refer to Teva Pharmaceuticals USA, Inc. and Teva Pharmaceutical Industries, Ltd.) is a corporation incorporated under the laws of the State of Delaware, with its principal place of business at 1090 Horsham Road, North Wales, PA 19454. [Revised Final Pretrial Order, Stipulated Fact 2.]

3. Merck & Co., Inc. (Merck & Co., Inc., Merck Sharpe & Dohme Pharmaceuticals, SRL, and Merck Frosst Canada will collectively be referred to as "Merck") is the holder of approved New Drug Application ("NDA") No. 20-829 for certain dosage forms in which the active ingredient is montelukast sodium; these products are sold under the trademark Singulair®. [Revised Final Pretrial Order, Stipulated Fact 3.]

4. MSD is the owner of United States Patent No. 5,565,473 ("the '473 patent") and all rights therein. [Revised Final Pretrial Order, Stipulated Fact 4.] The '473 patent, entitled "Unsaturated Hydroxyalkylquinoline Acids as Leukotriene Antagonists," is generally directed to leukotriene antagonists. [Revised Final Pretrial Order, Stipulated Fact 67.]

B. The Patent-in-Suit

5. The sole patent-in-suit is the '473 patent. [Revised Final Pretrial Order, Stipulated Fact 23.]

6. The named inventors of the '473 patent are Michel Belley, Dr. Serge Leger, Dr. Marc Labelle, Dr. Patrick Roy, Dr. Yi B. Xiang, and Dr. Daniel Guay. [Revised Final Pretrial Order, Stipulated Fact 24; TEX 3001.]

7. The '473 patent was issued on October 15, 1996. [Revised Final Pretrial Order, Stipulated Fact 25.]

8. Claim 18 is directed to a specific compound, montelukast, or its pharmaceutically acceptable salts. [Revised Final Pretrial Order, Stipulated Fact 32.]

9. Claim 19 is directed to the sodium salt of montelukast. [Revised Final Pretrial Order, Stipulated Fact 33.]

10. Claim 20 is directed to a pharmaceutical composition comprising a pharmaceutical carrier and an effective amount of the compound of claim 18. [Revised Final Pretrial Order, Stipulated Fact 34.]

11. Claim 21 is directed to a method of preventing the action of leukotrienes in a mammal by administering an effective amount of the compound of claim 18. [Revised Final Pretrial Order, Stipulated Fact 35.]

12. Claim 22 is directed to a method of treating asthma in a mammal by administering to a mammal in need of such treatment a therapeutically effective amount of a compound of claim 18. [Revised Final Pretrial Order, Stipulated Fact 36.]

C. Teva's Abbreviated New Drug Applications

13. Teva was aware of the '473 patent by June of 2000. [Goshko Dep. Tr. 44:9-21.]

14. Teva had contemplated filing an Abbreviated New Drug Application ("ANDA") on montelukast as early as 2000. [Payne Dep. Tr. 86:2-16.]

15. In her deposition, Anne Payne testified that brand product market size is "absolutely" a factor that Teva considers in deciding whether to file an ANDA for a drug. [Payne Dep. Tr. 126:16-21.]

16. Ms. Payne also testified that any drug with over $2 billion dollars in sales would be a high priority for Teva. [Payne Dep. Tr. 132:13-18.]

17. Teva sought an analysis of the '473 patent from Kenyon & Kenyon, LLP in June 2005. [Goshko Dep. Tr. 46:2-11; 47:6-21.] The opinion was rendered on June 21, 2005. [Goshko Dep. Tr. 47:18-21.]

18. Defendant Teva filed ANDA No. 78-605 (for generic tablets containing 10 mg of montelukast sodium) with the Food and Drug Administration ("FDA") as a paragraph III certification pursuant to Title 21, United States Code § 355(j)(2)(A)(vii)(III) on November 13, 2006. [Revised Final Pretrial Order, Stipulated Fact 55.] The fact that the ANDA included a paragraph III certification meant that Teva did not challenge the validity or enforceability of the '473 patent. [Goshko Dep. Tr. 68:2-15; TEX 3003.0048, 0067-68.]

19. On December 22, 2006, Defendant Teva USA filed ANDA No. 78-723 for generic tablets containing 4 mg and 5 mg of montelukast sodium, and included a paragraph III certification under Title 21, United States Code § 355(j)(2)(vii)(IV). [Revised Final Pretrial Order, Stipulated Fact 58; TEX 3004.0001, 0020.]

20. Mr. Goshko testified that, in general, Teva would make a lot more money by switching a paragraph III certification to a paragraph IV certification [Goshko Dep. Tr. 84:20-85:8], and a Teva ANDA for montelukast with a paragraph IV certification would have more potential value to Teva than the original paragraph III certification. [Goshko Dep. Tr. 87:11-16.]

21. Teva is a commercial company, which means that they are in the business to make money. [Payne Dep. Tr. 120:25-121:1; 121:4-8.]

22. No later than February 23, 2007, Merck received notice that Defendant Teva USA had amended Abbreviated New Drug Application ("ANDA") No. 78-605 to include a paragraph IV certification pursuant to Title 21, United States Code § 355(j)(2)(A)(vii), with the Food and Drug Administration ("FDA") for generic tablets containing 10 mg of montelukast sodium. [Revised Final Pretrial Order, Stipulated Facts 5, 7.]

23. On or about April 2, 2007, Merck received notice that Defendant Teva USA had amended ANDA No. 78-723 to include a paragraph IV certification pursuant to Title 21, United States Code § 355(j)(2)(A)(vii), with the FDA for generic chewable tablets containing 4 mg and 5 mg of montelukast sodium. [Revised Final Pretrial Order, Stipulated Fact 15.]

24. A detailed statement accompanied both of these notices. [TEX 3005, 3006.]

25. Marc Goshko, Teva's Executive Director of Legal Affairs and one of the Teva employees who works on FDA regulatory issues [Goshko Dep. Tr. 6:22-7:7], testified that Brinks Hofer Gilson & Lione (Brinks Hofer), Teva's outside counsel in this case, prepared the detailed statement that accompanied Teva's paragraph IV certification on the 19th and 20th of February 2007. [Goshko Dep. Tr. 27:6-10; 28:10-14.]

26. Prior to Teva's assignment of the detailed statement to Brinks Hofer, which occurred around February 19, 2007, Brinks Hofer was working on an analysis of the '473 patent for Teva. [Goshko Dep. Tr. 59:1-16.] Teva first requested that Brinks Hofer analyze the '473 patent sometime in 2006. [*Id.* at 60:18-61:2.]

27. Teva received an opinion from Brinks Hofer on or around February 19, 2007. [Goshko Dep. Tr. 63:9-21.]

28. Teva made the decision to change its paragraph III certification to a paragraph IV certification on or after February 19, 2007, and notified Merck shortly thereafter. [Goshko Dep. Tr. 73:5-11; TEX 3005 and 3006.]

29. On April 3, 2007, Merck filed a complaint in the United States District Court for the District of New Jersey, Civil Action No. 07-1596 (GEB), alleging

infringement of the '473 patent under 35 U.S.C. § 271(e)(2)(A) based on Defendant Teva USA's filing of ANDA No. 78-605. [Revised Final Pretrial Order, Stipulated Fact 8.]

30. Pursuant to Title 21, United States Code § 355(j)(5)(B)(iii), the filing of Merck's complaint stayed the potential FDA approval of Teva's ANDA No. 78-605 for thirty months from the date that Merck received notice that Teva USA filed ANDA No. 78-605. [Revised Final Pretrial Order, Stipulated Fact 9.]

31. The thirty month stay on the potential FDA approval of Teva's ANDA No. 78-605 expires on or about August 23, 2009. [Revised Final Pretrial Order, Stipulated Fact 10.]

32. On May 29, 2007, Teva filed its Answer, Affirmative Defenses, and Counterclaims to Merck's complaint based on Defendant Teva's filing of ANDA No. 78-605. [Revised Final Pretrial Order, Stipulated Fact 11.]

33. On June 18, 2007, Merck entered its Reply to the Counterclaims of Teva USA and Teva Ltd. related to Merck's complaint based on Teva's filing of ANDA No. 78-605. [Revised Final Pretrial Order, Stipulated Fact 12.]

34. On May 14, 2007, Merck filed a complaint in the United States District Court for the District of New Jersey (Civil Action Number 07-2264 (GEB)), alleging infringement of the '473 patent under 35 U.S.C. § 271(e)(2)(A), based on Teva's filing of ANDA No. 78-723. [Revised Final Pretrial Order, Stipulated Fact 16.]

35. On June 12, 2007, Teva filed its Answer, Affirmative Defenses, and Counterclaims to Merck's complaint based on Teva's filing of ANDA No. 78-723. [Revised Final Pretrial Order, Stipulated Fact 17.]

36. On July 2, 2007, Merck entered its Reply to the Counterclaims of Teva related to Merck's complaint based on Defendant Teva's filings of ANDA No. 78-723. [Revised Final Pretrial Order, Stipulated Fact 18.]

37. On August 6, 2007, Merck filed its First Amended Complaints in Case Nos. 07-1596 (GEB)(JJH) and 07-2264 (GEB)(JJH) regarding the alleged infringement of the '473 patent based on Defendant Teva's filing of ANDA Nos. 78-605 and 78-723. [Revised Final Pretrial Order, Stipulated Fact 19.]

38. On August 7, 2007, the Court ordered Civil Action Numbers 07-1596 (GEB), related to Merck's complaint based on Teva's filing of ANDA No. 78-605, and 07-2264 (GEB), related to Merck's complaint based on Defendant Teva's filing of ANDA No. 78-723, consolidated as Civil Action Number 07-1596 (GEB) for all purposes. [Revised Final Pretrial Order, Stipulated Fact 20.]

39. On August 17, 2007, Defendant Teva filed its Answer, Affirmative Defenses, and Counterclaims to Merck's First Amended Complaint based on Teva's filing of ANDA No. 78-723. [Revised Final Pretrial Order, Stipulated Fact 21.]

40. On August 30, 2007, Merck entered its Replies to the Counterclaims of Teva related to Merck's First Amended Complaints in Case Nos. 07-1596 (GEB)(JJH) and 07-2264 (GEB)(JJH). [Revised Final Pretrial Order, Stipulated Fact 22.]

41. Defendant Teva was aware of the '473 patent before February 20, 2007. [Revised Final Pretrial Order, Stipulated Fact 57.]

42. Defendant Teva was aware of the '473 patent at the time that Teva filed ANDA No. 78-605 with the FDA. [Revised Final Pretrial Order, Stipulated Fact 59.]

43. Teva was aware at the time that Teva filed ANDA No. 78-605 with the FDA that doing so constituted an act of patent infringement under Title 35, United States Code, § 271(e)(2)(A). [Revised Final Pretrial Order, Stipulated Fact 60.]

44. Defendant Teva was aware of the '473 patent at the time that Teva filed ANDA No. 78-723 with the FDA. [Revised Final Pretrial Order, Stipulated Fact 61.]

45. Defendant Teva was aware at the time that Teva filed ANDA No. 78-723 with the FDA that doing so constituted an act of patent infringement under Title 35, United States Code, § 271(e)(2)(A). [Revised Final Pretrial Order, Stipulated Fact 62.]

D. Asthma is a Serious and Deadly Disease

46. Asthma is a chronic inflammatory disease that affects the lower airways of the lungs. [T. Tr., Feb. 25, 2009 P.M. 37:17-18 (Meltzer); TEX 3183.0002.] Asthma is a complex human disease. [T. Tr., Feb. 23, 2009 A.M. 46:14-15 (Young).]

47. Asthma is a serious condition and results in substantial burdens on society as a whole. Asthma is a very prevalent disease: there are probably 300 million people suffering from asthma worldwide, of which 20 to 25 million reside in the United States. [T. Tr., Feb. 25, 2009 P.M. 38:15-18 (Meltzer).] Asthma results in 250,000 deaths each year, including 4,000 deaths a year in the United States. [*Id.*]

48. In the United States alone, asthma is responsible for 500,000 hospitalizations, 2 million emergency room visits, and 9 million office visits. [T. Tr., Feb. 25, 2009 P.M. 38:17-20 (Meltzer).] This translates to about 14 million missed days of work and 14 million missed days of school. [*Id.* at 28:24-29:2.] And these numbers do not account for the vast number of asthma sufferers who do not miss days at work or

school but are nonetheless rendered substantially less effective by symptoms of asthma. [*Id.* at 39:2-7.]

49. The total cost to society resulting from asthma is estimated to be about $20 billion a year. [T. Tr., Feb. 25, 2009 P.M. 39:8-9 (Meltzer).]

50. Asthma can be triggered by a number of stimuli, including allergens, irritants such as tobacco smoke or pollutants, respiratory infections, weather conditions, exercise, and even certain medications. [T. Tr., Feb. 25, 2009 P.M. 37:18-23 (Meltzer).]

51. These stimuli cause the release of mediators and inflammatory cells, which then result in the physical symptoms associated with asthma. [T. Tr., Feb. 25, 2009 P.M. 37:23-38:11 (Meltzer).] The characteristic symptoms of asthma are bronchoconstriction, dyspnea (shortness of breath), cough, chest congestion, excessive production of mucus, hypersensitivity of the airways, swelling of the airways, and lung inflammation. [T. Tr., Feb. 25, 2009 P.M. 38:3-11; TEX 3183.0002.]

52. Asthma can be characterized by class, either intermittent or persistent. [T. Tr., Feb. 25, 2009 P.M. 40:16-18 (Meltzer).] Within the persistent category, asthma can be labeled as mild, moderate, or severe. [*Id.* at 40:18-19.] The factors which determine what class of asthma a particular person is suffering from include the frequency of the symptoms, the person's ability to physically perform all of their activities, whether the person requires a "rescue" inhaler for acute attacks, whether the person has normal lung function, and the frequency of exacerbations. [*Id.* at 40:22-41:6 (Meltzer).]

E. The Relationship Between Asthma and LTD_4

53. In the 1930's and 1940's, scientists studying the lungs of guinea pigs discovered that a particular substance, which they called the slow reacting substance of anaphylaxis ("SRS-A"), produced in the guinea pigs' lungs caused the contraction of smooth muscle tissues in the lungs. [Revised Final Pretrial Order, Stipulated Fact 63.]

54. SRS-A comprises three leukotrienes: LTC_4, LTD_4, and LTE_4. [TEX 0008.0004; T. Tr., Feb. 23, 2009 A.M. 45:3-5 (Young).]

55. Leukotrienes, and specifically LTD_4, are substances that are produced in the lung and other organs. [T. Tr., Feb. 23, 2009 A.M. 45:2-3 (Young).]

56. Leukotrienes bind with receptors in the lung. [TEX 0008.0004 ("The biological activities of the leukotrienes are mediated by specific receptors and in human lung the actions of the peptide leukotrienes are mediated by a common receptor (or receptor).").]

57. LTD_4 is the most active leukotriene. [TEX 0008.0004 (3158).]

58. In fact, LTD_4 has the greatest activity of the four types of leukotrienes known, which means that, on a weight-for-weight basis, it has the most potent activity in contracting muscles and stimulating the LTD_4 receptor. [T. Tr., Feb. 23, 2009 A.M. 45:15-17, 46:16-20 (Young).]

59. LTD_4 is composed of a peptide and a lipid and is a very unusual compound. [T. Tr., Feb. 23, 2009 A.M. 45:3-5 (Young).]

60. The receptor that binds LTD_4 is the cysteinyl leukotriene receptor, or CysLT1 receptor, and is sometimes referred to as the LTD_4 receptor. [Revised Final Pretrial Order, Stipulated Facts 64, 65.]

61. When LTD_4 binds with the LTD_4 receptor, the muscles of the lungs contract, or spasm. [TEX 3283.0003.] LTD_4 also stimulates the production of mucus and causes changes in vascular permeability, resulting in inflammation and swelling. [TEX 3183.0003; T. Tr., Feb. 25, 2009 P.M. at 53:20-23 (Labelle).]

62. An LTD_4 antagonist interacts with the receptor molecules in muscles and tissue, occupying the same site as the LTD_4 molecule would. The interaction between an LTD_4 antagonist and the LTD_4 receptor does not cause the physiological reaction that LTD_4 causes. Rather, an LTD_4 antagonist prevents LTD_4 from interacting with the receptor, and blocks the effects that LTD_4 has on muscle tissue. [T. Tr., Feb. 23, 2009 A.M. 47:10-15.]

63. The structure of the LTD_4 receptor was unknown for the duration of Merck's LTD_4 antagonist program. [T. Tr., Feb. 23, 2009 A.M.47:3-7 (Young).]

64. The structure of the LTD_4 receptor remains unknown today. [T. Tr., Feb. 26, 2009 33:13-23 (Jorgensen).]

F. Allergic Rhinitis Causes Much Suffering

65. Allergic rhinitis is a broad term that subsumes both seasonal allergic rhinitis and perennial allergic rhinitis. The major difference between these two conditions is the nature of the allergens. [Philip Dep. Tr. 58:18-23.]

66. Seasonal allergic rhinitis affects patients who are allergic to pollen (or other allergens) that is present in the spring or fall. Seasonal allergic rhinitis is not considered to be a year-round condition. [Philip Dep. Tr. 58:24-59:4.]

67. Perennial allergic rhinitis is related to a patient's allergies to substances that are present year-round and often found indoors. These types of allergies result in year-round symptoms. [Philip Dep. Tr. 59:5-9.]

68. Singulair® pharmaceutical products have been approved by the FDA for the treatment of both seasonal and perennial allergic rhinitis. [Philip Dep. Tr. 59:10-14.]

69. Allergic rhinitis is very common, affecting approximately 20 percent of the population. [T. Tr., Feb. 25, 2009 P.M. 51:1-2 (Meltzer).]

70. The social burdens of allergic rhinitis include 9 million office visits per year in the Unites States and significantly compromised quality of life. [T. Tr., Feb. 25, 2009 P.M. 51:7-20 (Meltzer).] In the 2006 Allergies in America survey of people suffering from allergic rhinitis, 85 percent of those surveyed said that allergic rhinitis impacted their lives, and 40 percent of those surveyed said that the impact was moderate to severe. [*Id.*] In all, the money spent on doctors and medicines related to allergic rhinitis has been estimated to be approximately $7 billion a year. [*Id.* at 52:10-12.]

G. The Relationship Between Allergic Rhinitis and LTD_4

71. The symptoms of allergic rhinitis manifest according to very similar mechanisms as those seen in asthma, except that these mechanisms occur in the lining of the nose. [T. Tr., Feb. 25, 2009 P.M. 21:4-13 (Meltzer).] Histamine is the primary mediator of allergic rhinitis, but LTD_4 is also present. [*Id.* at 21:15-18.]

72. With both asthma and allergic rhinitis, the more severe the disease, the greater number of leukotrienes are present. [T. Tr., Feb. 25, 2009 P.M. 54:9-11 (Meltzer).]

II. Merck's Herculean Efforts to Develop LTD_4 Antagonists

73. Dr. Robert Young worked for Merck Frosst Canada for 29 years, from 1977 to 2006. [T. Tr., February 23, 2009 A.M. 42:4-9; 108:14-17 (Young).]

74. After the structure of leukotrienes was discovered in 1979, Dr. Young and others at Merck started a project relating to leukotrienes. [T. Tr., Feb. 23, 2009 A.M. 43:3-5 (Young).]

75. Dr. Young's early role in the leukotriene project was to make leukotrienes. That effort involved setting up assays and creating screening mechanisms. [T. Tr., Feb. 23, 2009 A.M. 43:9-11 (Young).]

76. Dr. Young became responsible for managing the leukotriene program at Merck in or around 1984. [T. Tr., February 23, 2009 A.M. 90:1-5.]

77. Dr. Marc Labelle worked for Merck Frosst Canada for 15 years, from 1985 to 2000. [T. Tr., February 23, 2009 A.M. 129:23-24 (Labelle).]

78. From 1988 to 1994, Dr. Labelle was the project leader for Merck's leukotriene antagonist program. [T. Tr., Feb. 23, 2009, A.M. 129:23-130:5; 131:3-4.]

79. In the first few years of the leukotriene project, the chemists focused their work on creating leukotrienes and their metabolites. [T. Tr., Feb. 23, 2009 A.M. 43:15-20 (Young).]

80. Dr. Young led a group of four chemists during the early years of the leukotriene project, and eventually took full responsibility for the leukotriene program. [T. Tr., Feb. 23, 2009 A.M. 43:25-44:1, 44:17-19 (Young).]

81. Ten to twelve scientists were involved in the leukotriene project at its inception. [T. Tr., Feb. 23, 2009 A.M. 48:1-4 (Young).]

82. The leukotriene project grew over time, and involved 20 some chemists and many biologists during the project's most active years. [T. Tr., Feb. 23, 2009 A.M. 48:15-18 (Young).] The total number of people working on the project during the 1990-1991 time frame was between 40 and 45 just at Merck Frosst Canada. [T. Tr., Feb. 23, 2009 A.M. 132:4-7 (Labelle).]

83. The goal of the project was to create a compound that would antagonize the LTD_4 receptor in a potent manner, allowing for the compound to be administered in relatively low doses. The compound would ideally be administered orally and would have a half-life allowing for once-a-day dosing. And the compound would have to be safe, particularly because it would be used to treat a chronic disease – asthma – indefinitely. [T. Tr., Feb. 23, 2009 A.M. 49:14-50:2 (Young); *see also* Guay Dep. Tr. 16:3-5 (Inventor Daniel Guay explained that the purpose of Merck's LTD_4 antagonist program was to find a molecule that could be useful as a new therapy for asthma.).]

84. In the early years of the project, LTD_4 served as a lead compound for some pharmaceutical development teams. [T. Tr., Feb. 23, 2009 A.M. 50:6 (Young).] Other teams, including Merck, started with the only known LTD_4 antagonist, FPL-55712. [T. Tr., Feb. 23, 2009 A.M. 50:7-11, 50:22-51:2 (Young).]

85. Merck tested FPL-55712 (a known antagonist of SRS-A) and confirmed that it was an antagonist, but this testing also showed that FPL-55712 had a very short half-life, was not well absorbed, and what was absorbed was rapidly metabolized. [T. Tr., Feb. 23, 2009 A.M. 51:5-8 (Young).]

86. Merck also screened its library for potential lead compounds. This involved going through the Merck collection of compounds that was available to the research team, and the team would look for compounds that might have a similar structure to FPL-55712, for example. This screening process was not efficient, and the team had to use their intuition in deciding which compounds to select for testing. [T. Tr., Feb. 23, 2009 A.M. 52:6-16 (Young).]

87. Dr. Young would obtain a printout of the compounds in the Merck library, and would spend weekends reviewing the list of compounds, trying to come up with 1,000 or so compounds for testing out the approximately 100,000 compounds available. [T. Tr., Feb. 23, 2009 A.M. 53:16-23.]

88. To test these selected compounds, the chemists developed a screen using tissue from a guinea pig or rat. The tissue was placed in a physiological bath, and leukotrienes were added in minute quantities, causing the tissue to contract. The chemists then added a potential leukotriene antagonist and viewed the results, if any. If the addition of the antagonist resulted in fewer contractions, the chemists considered it to be a promising compound. [T. Tr., Feb. 23, 2009 A.M. 52:24-53:1-8 (Young).]

89. This screening process was labor intensive. [T. Tr., Feb. 23, 2009 A.M. 54:1-3 (Young).]

90. If the initial screening process showed a compound to have antagonist activity, the chemists would then dose the compound in a rat and determine whether it had a reasonable half life in the rat. [T. Tr., Feb. 23, 2009 A.M. 55:6-11 (Young).]

91. If the compound was absorbed and had a reasonable half-life, the compound would then be tested in asthmatic rats. [T. Tr., Feb. 23, 2009 A.M. 55:20-22 (Young).]

92. When the chemists tested the compound in asthmatic rats, the chemists would look to see whether the compound reduced asthma-like symptoms, and would also look for any obvious toxicity issues. [T. Tr., Feb. 23, 2009 A.M. 56:13-21 (Young).]

93. Toxicity could be caused by the compound itself, or by metabolites of the compound. [T. Tr., Feb. 23, 2009 A.M. 57:3-4 (Young).]

94. Dr. Young testified that, because metabolism of a compound is difficult to predict, the chemists' approach was "normally to actually see what happens, rather than predict what happens." [T. Tr., Feb. 23, 2009 A.M. 57:17-20.]

95. Every time that a chemist made a compound, the compound was given an "L" number. [T. Tr., Feb. 23, 2009 A.M. 58:11-14 (Young).]

A. First Generation Merck Compounds

96. Of the compounds developed in the first few years of Merck's LTD_4 antagonist program, compounds L-648,051 and L-649,923 were deemed to be potentially useful. Dr. Young testified that those compounds worked relatively well on all of the chemists' animal models and "it was predicted that the doses based on those models would not be . . . too large, assuming everything worked as planned." The compounds "were brought forward as development candidates, . . . synthesize[d] in large quantities, taken to toxicology, safety assessment." The compounds then went through multi-week and multi-month safety assessments, and then were finally formulated and brought to clinical trials. [T. Tr., Feb. 23, 2009 A.M. 58:5, 59:2-10.]

97. In order to bring a compound to clinical trials, the chemists were required to conduct in vitro (test tube) and animal tests, compile the test results and present the entire package to a development committee. That data included several assays that tested for toxicity and other adverse side effects. The package presented to the development committee also included a potential way to make the compound, as well as data demonstrating that the compound had oral activity and oral absorption. [T. Tr., Feb. 23, 2009 A.M. 59:16-25 (Young).]

98. In 1985, Merck initiated the first clinical trial with one of its promising compounds, L-648,051. [T. Tr., Feb. 23, 2009 A.M. 59:10 (Young).]

99. After a compound was approved for development (*i.e.*, clinical trials), the development team would further study and define the metabolism of the compound, and would find a way to develop the compound on a larger scale. The team would then create kilograms of the compound, which allowed for it to be used in "a safety assessment study, usually in rats and other non-rodent animal[s], often a dog, sometimes a monkey, where it would be tested for, in those days, usually three months toxicology testing." [T. Tr., Feb. 23, 2009 A.M. 60:3-23 (Young).]

100. L-648,051 was only bio-available by aerosol, so the development team also had to develop a dosage and put it in a powder aerosol, with the right chemical properties required for an aerosol. [T. Tr., Feb. 23, 2009 A.M. 61:1-6 (Young).]

101. Human trials first involved single doses to non-asthmatic volunteers. The chemists and development team observed these volunteers after a dose was administered to see if the subjects developed any obvious side effects. This process took several months, and required the chemists and development team to slowly raise the amount of active ingredient in the single dose to what was thought to be a viable maximum. [T. Tr., Feb. 23, 2009 A.M. 61:7-15 (Young).]

102. If single doses were tolerated by the non-asthmatic volunteers, the compound would proceed to "multi-day testing, usually for a week or so or maybe longer, several weeks, and again, in normal volunteers to determine if it was tolerated." [T. Tr., Feb. 23, 2009 A.M. 61:7-15 (Young).]

103. If the compound was shown to be absorbed and well-tolerated in multi-day testing in non-asthmatic volunteers, it would then be tested in asthmatic volunteers, first as a single dose test and then as a multi-dose test. [T. Tr., Feb. 23, 2009 A.M. 61:16-20 (Young).]

104. L-648,051 was tolerated in asthmatic volunteers. [T. Tr., Feb. 23, 2009 A.M. 61:23-24 (Young).]

105. The chemists determined that the amount of L-648,051 that was required to result in only a small reduction of bronchial constriction was too large, and

the effect was not adequate. L-648,051 was abandoned. [T. Tr., Feb. 23, 2009 A.M. 62:14-18 (Young).]

106. L-649,923 also progressed to clinical trials. The compound was ultimately tested in asthmatics, but "it did not show efficacy of significance in [treating] asthma." [T. Tr., Feb. 23, 2009 A.M. 62:22-63:21 (Young).]

107. The chemists decided that they needed a compound at least three times better than L-648,051 and L-649,923. [T. Tr., Feb. 23, 2009 A.M. 64:7-8 (Young).]

B. Second Generation Merck Compounds

108. While L-648,051 and L-649,923 were in development, the chemists continued to pick compounds and screen those compounds for potential leads. [T. Tr., Feb. 23, 2009 A.M. 64:15-18 (Young).]

109. After L-648,051 and L-649,923 failed trials, the chemists decided to look at L-603,000 more closely as a potential lead. Dr. Young liked this compound because "it was very simple, small molecule, not very much adorned. And [the chemists] thought [they] could perhaps evolve it by adding more elements. And so over a number of years, [the chemists] made many analogs trying to understand what parts of the molecule were important, which were not, where [the chemists] could add groups." [T. Tr., Feb. 23, 2009 A.M. 65:1-14.]

110. L-603,000 did not have "an acidic group, which [the chemists] felt was important for binding leukotrienes and presumably leukotriene antagonist[s] to see what [they] had seen in earlier compounds. And so [they] made compounds [(analogs of L-603,000)] adding on a chain with an acid of various lengths and found . . . that it actually did improve the activity." [T. Tr., Feb. 23, 2009 A.M. 65:15-21 (Young).]

111. The chemists "also found that inputting a chlorine atom [on] the quinoline ring actually gave [L-660,711] a boost in activity, a surprising boost because [the chemists] had actually put it in there to try and block potential metabolic sites. [The chemists] were very pleased to find that [the chlorine atom] also increased the [compound's] activity." [T. Tr., Feb. 23, 2009 A.M. 66:14-18 (Young).]

112. The addition of a second side chain was "stimulated by some work done by Smith Kline [&] French laboratories where they had used a similar element." This modification resulted in "a very good boost in activity, but the compound itself didn't show the kind of overall activity or efficacy that the [chemists] expect[ed]." [T. Tr., Feb. 23, 2009 A.M. 66:22-67:5 (Young).]

1. L-660,711

113. The Merck chemists continued to modify the compound. The chemists converted one of the two acid groups to an amide, and made compounds containing a variety of amides. The compound that showed the best results was L-660,711. [T. Tr., Feb. 23, 2009 A.M. 67:12-15 (Young).]

114. The chemists had synthesized "hundreds and hundreds of compounds," before they came up with L-660,711. [T. Tr., Feb. 23, 2009 A.M. 65:22-66:7 (Young).]

115. The pre-development data showed that L-660,711 was "very potent and effective in animal studies. It was well absorbed. It's half-life was quite good." [T. Tr., Feb. 23, 2009 A.M. 67:20-23 (Young).]

116. After L-660,711 was accepted for development, it was given the label MK-571. [T. Tr., Feb. 23, 2009 A.M. 65:22-66:7 (Young).]

117. Dr. Young testified that MK-571 "proved to be very safe at least in the animal studies initially." [T. Tr., Feb. 23, 2009 A.M. 68:1-2.]

118. Clinical trials for MK-571 were initiated in 1989. [T. Tr., Feb. 23, 2009 A.M. 68:3-4 (Young).]

119. The clinical trials showed that MK-571 "had a significant effect on asthmatics and actually reversed some of the bronchial constriction either induced by a challenge in asthmatics or in fact by normal asthmatics who are not in a challenged situation." [T. Tr., Feb. 23, 2009 A.M. 68:7-13 (Young).]

120. Unfortunately, longer term animal toxicity studies showed liver side effects in rats – specifically, changes in liver weight and liver enzymes. These changes had previously been associated with a potential for tumorogenicity; liver tumors. [T. Tr., Feb. 23, 2009 A.M. 68:19-23 (Young).]

121. The Merck team decided to abandon MK-571, in part because the toxicity indications meant that the team would have to conduct extensive carcinogenicity studies, which take many years. Dr. Young testified that carcinogenicity studies were troublesome because "[b]y the time you find out you have a problem . . . years have gone by. And you don't want to wait that long." [T. Tr., Feb. 23, 2009 A.M. 69:1-4.]

2. MK-0679

122. MK-571 was composed of two isomers, the R-isomer and the S-isomer. [T. Tr., Feb. 23, 2009 A.M. 69:13-15 (Young); Feb. 23, 2009 P.M. 19:5-9 ("One of th[e]s[e] is like a right hand, the other is like a left hand.") (Labelle).]

123. The chemists discovered that the R-isomer of MK-571 did not have the adverse liver effects seen in clinical trials. [T. Tr., Feb. 23, 2009 A.M. 70:2-4 (Young).]

124. The Merck chemists isolated the R-isomer and prepared it as a separate compound. This compound was labeled L-668,019, or MK-0679. After the compound showed promise in treating asthma, it was given the name verlukast. [T. Tr., February 23, 2009 A.M. 70:5-14 (Young).]

125. In clinical trials, verlukast proved to be just as efficacious as MK-571. Dr. Young explained that the compound "went through very long term animal studies, up to a year. And without any liver effects." [T. Tr., February 23, 2009 A.M. 70:15-21.]

126. "[I]n the long term human trials, after six weeks, [the chemists] saw human liver effects in a small number [three to four percent] of patients." Because the goal of the project was to create a drug that could be used in treating children, the liver effects, however small, could not be tolerated. As a result, Merck halted development of MK-679. [T. Tr., Feb. 23, 2009 A.M. 70:22-71:9 (Young).]

3. The Long and Arduous Path to Montelukast

127. When Dr. Labelle joined Merck's leukotriene program in 1988, MK-571 was moving towards clinical trials, and the goal of the program at that time was to find a backup for MK-571; that is, a compound that could "take the place of MK-571 if there is a problem in the clinic or in toxicology." [T. Tr., Feb. 23, 2009, P.M. 4:12-13, 4:16-21 (Labelle).]

128. The Merck chemists decided to make the backup compound to MK-571 "as different as possible." [T. Tr., Feb. 23, 2009 A.M. 4:23-25 (Labelle).]

129. The chemists took a trial by error approach, adopting changes that, after testing, showed beneficial properties, and then exploring additional options for further benefits. [T. Tr., Feb. 23, 2009 P.M. 49:12-17 (Labelle).]

130. This was consistent with their approach throughout the program: The Merck chemists used a trial-and-error method to develop more effective LTD_4 antagonists. [Guay Dep. Tr. 18:12-19 ("There were some molecules that had some affinity for the receptor or some potency. And so it's like when you play with Lego blocks. You just build on and modify. So looking at the structure of our molecules, we would try and modify different areas in the molecule to improve the overall profile."); *see id.* at 21:4-20.]

131. In looking for a back-up to MK-571, the chemists began by changing the linker between the quinoline ring and the phenyl ring. The team tried a variety of different linkers. The resulting compounds were less potent, but still had good activity. [T. Tr., Feb. 23, 2009, P.M. 5:6-12; 5:14-18 (Labelle).]

132. The chemists then looked at the sulfur atom in the amide-containing side chain of L-660,711 (which Teva has referred to as the "Q^2" side chain).

The chemists replaced the sulfur with a carbon atom, and found that this did not change the potency of the compound. [T. Tr., Feb. 23, 2009 P.M. 5:20-6:3 (Labelle).]

133. After removing a sulfur atom, the chemists added a phenyl ring on the Q^2 side chain. Dr. Labelle testified that the chemists could have added a variety of different compounds here, and in fact did, but the phenyl ring was the change that was retained. The chemists found that this addition helped regain some of the potency lost when the linker between the phenyl ring and the quinoline ring was changed. [T. Tr., Feb. 23, 2009 P.M. 6:12-21 (Labelle).]

134. The chemists also recognized that the two side chains were interchangeable, and experimented with the amide on the Q^1, sulfur-containing side chain. [T. Tr., Feb. 23, 2009 P.M. 6:25-7:13 (Labelle).]

135. The chemists decided to test the resulting compound in animals. They found that the compound was potent, but had a short half-life. [T. Tr., Feb. 23, 2009 P.M. 7:14-8:4 (Labelle).]

136. The chemists believed that the compound was being metabolized too quickly in the animals, resulting in a short half-life. [T. Tr., Feb. 23, 2009 P.M. 8:17-24 (Labelle).]

137. A short half-life means that the compound does not stay in the body long enough, and requires a patient to "take pills many times a day. This is not desirable." [T. Tr., Feb. 23, 2009 P.M. 9:1-4 (Labelle).]

138. The chemists attempted to solve the metabolism issue first by substituting different moieties in the alpha position on the Q^1 side chain. This was one of many approaches the chemists could have taken. [T. Tr., Feb. 23, 2009 P.M. 10:2-17; *see also* TEX 3183.0013.]

139. The chemists ran multiple assays to test each substitution. [T. Tr., Feb. 23, 2009 P.M. 10:21-11:4 (Labelle).]

140. As the program progressed, the chemists developed new assays. "The introduction of new assays was a learning process." [TEX 3183.0007.]

141. The Merck chemists also attempted to pull metabolites from the blood of animal test subjects. The Merck chemists realized that the amide functionality was undergoing metabolism, meaning that the team would have to move away from using amides. [T. Tr., Feb. 23, 2009 P.M. 11:11-24 (Labelle); TEX 3183.0012-14.]

i. Replacing the Amides

142. The chemists first tried other amides in an effort to avoid the metabolism problem. [T. Tr., Feb. 23, 2009 P.M. 14:1-15:1 (Labelle).]

143. The chemists tried about 15 different amides; these other amides did not solve the metabolism problem. [T. Tr., Feb. 23, 2009 P.M. 15:14-16 (Labelle).]

144. The Merck chemists then substituted carboxylic acids for the amides. The acids also did not solve the metabolism problem. [T. Tr., Feb. 23, 2009 P.M. 15:21-25 (Labelle).]

145. The chemists then added in tetrazoles in place of the acids. Tetrazoles are extremely polar groups. Like the other molecules, the tetrazole compound was potent, but did not have the half-life that the chemists were looking for. [T. Tr., Feb. 23, 2009, P.M. 16:2-4 (Labelle).]

146. The concept with these various substitutions was to stay with very polar groups, since M-571 included a very polar group and did not present the same half-life problems. [T. Tr., Feb. 23, 2009 P.M. 16:19-21 (Labelle); TEX 3183.0016.]

147. The chemists then tried sulfonamides and inverse sulfonamides, carbonates, and nitriles, which are all also very polar groups. [T. Tr., Feb. 23, 2009 P.M. 16:22-17:2 (Labelle).]

148. The chemists then moved to less polar groups, including sulfones, esthers, alcohols, ketones, oxides, isopropyl, and hydrogen, roughly in that order. [T. Tr., Feb. 23, 2009 P.M. 17:3-14 (Labelle).]

149. From Dr. Labelle's perspective, the use of these less polar groups became logical only after the more polar groups were ruled out. [T. Tr., Feb. 23, 2009 P.M. 60:13-17.] The chemists spend two months on this specific modification before trying alcohols and other less polar groups. [T. Tr., Feb. 23, 2009 P.M. 64:3-22 (Labelle).] The results of this modification were not available outside of Merck. [T. Tr., Feb. 23, 2009 P.M. 64:23-25 (Labelle).]

150. For each group above, many distinct sub-groups were possible. For example, the chemists could add carbons to make the connection between the group and the phenyl ring longer, and the chemists could attach the group to any of the five points on the phenyl ring. [T. Tr., Feb. 23, 2009 P.M. 17:21-18:1 (Labelle).] The chemists could also use a variety of linkers for each altered compound. [*Id.* at 18:2-15.]

151. These tests occurred during 1989. [T. Tr., Feb. 23, 2009 P.M. 19:1-2 (Labelle).]

ii. First Use of a Tertiary Alcohol

152. The chemists found that one group, a tertiary alcohol, worked quite well in solving the half-life problem. [T. Tr., February 23, 2009 P.M. 20:3-10.]

153. The Merck chemists did not know why the tertiary alcohol was potent and contributed to the molecule's relatively longer half-life, they "just made it and found out." [T. Tr., Feb. 23, 2009 P.M. 20:11-15 (Labelle).]

154. Michel Belley made the compound containing the tertiary alcohol. [T. Tr., Feb. 23, 2009 P.M. 20:18-19 (Labelle).]

155. The compound containing the tertiary alcohol, L-691,054, exhibited liver toxicity in initial testing. [T. Tr., Feb. 23, 2009 P.M. 21:2, 21:9-12 (Labelle).] This type of toxicity had been associated with hepatic (liver) tumors. [*Id.* at 21:15-17.]

156. The chemists attempted to deal with the toxicity problem of L-691,054 by separating the compound into its four different isomers. The chemists found that the most potent isomers were also the most toxic. [T. Tr., Feb. 23, 2009 P.M. 22:2-10 (Labelle).]

157. The chemists decided to focus on an isomer with less potency and less toxicity. Dr. Labelle testified that one of the reasons for adopting this approach was that "[i]t was very difficult to run the [toxicity] assay, very tedious. So we decided to go for what we could solve, we thought, more rapidly by getting some potency back in the series that doesn't have the toxicity." [T. Tr., Feb. 23, 2009 P.M. 22:12-17.]

158. The Merck chemists reintroduced the olefin linker (the double bond) between the quinoline ring and the phenyl ring in an attempt to solve this problem. This modification was helpful in increasing potency. [T. Tr., Feb. 23, 2009 P.M. 23:8-21 (Labelle); TEX 3183.0021.]

159. The chemists would have attempted to develop the resulting compound, L-695,499, but they found that even though the compound did not cause liver toxicity, it did cause acute cardiac toxicity. [T. Tr., Feb. 23, 2009 P.M. 24:1-25:4 (Labelle); TEX 3183.0026.]

160. The chemists continued to modify the compound in an attempt to find a safe and potent LTD_4 antagonist. The chemists changed the carboxylic acid, made additional alpha substitutions, additional substitutions on the phenyl ring in the Q^2 position, and extended the chain length on the Q^2 side-chain. The chemists tested all of these variations. This work occurred during 1989 and 1990. [T. Tr., Feb. 23, 2009 P.M. 25:15-27:14; 29:1-3 (Labelle).]

161. The tests suggested that the least toxic molecule contained a methyl ketone at the 12 o'clock position on the phenyl ring in the Q^2 position. [T. Tr., Feb. 23, 2009 P.M. 29:14-21 (Labelle).]

162. This ketone-containing compound, L-669,392, was submitted to the development group, which began looking for an economical way to produce

additional quantities of the molecule. The compound was not as potent as the tertiary alcohol-containing compound, but it did not exhibit the same toxicity. [T. Tr., Feb. 23, 2009 P.M. 31:9-32:5 (Labelle).]

163. After L-669,392 was sent to development, the chemists again began looking for another backup compound. [T. Tr., Feb. 23, 2009 P.M. 33:5-7 (Labelle).]

iii. Resolving Toxicity Issues

164. The Merck chemists returned to the tertiary alcohol series and again attempted to resolve the toxicity issues. [T. Tr., Feb. 23, 2009 P.M. 33:18-34:9 (Labelle).]

165. Around this time, Dr. Anthony Ford Hutchinson, the Director of Pharmacology at Merck, left a paper on Dr. Labelle's desk that discussed the metabolism of carboxylic acids. Dr. Labelle explained that "this article had more to do with the normal metabolic pathways, nothing to do with enzyme induction, but it triggered a thought in my mind that maybe if we could alter this [compound] in such a way that it did not look like a natural fatty acid, maybe we would avoid enzyme induction [*i.e.*, liver toxicity]." [T. Tr., Feb. 23, 2009 P.M. 34:12-21.]

166. Though the paper that Dr. Ford Hutchinson gave Dr. Labelle had nothing to do with LTD_4 antagonists (and there was no indication in any published or unpublished literature that the Merck compounds were subject to beta oxidation), Dr. Labelle and the other chemists tried to modify the beta position of the tertiary alcohol-containing molecules in an attempt to solve the toxicity issues. [T. Tr., Feb. 23, 2009 P.M. T. Tr. 35:3-8 (Labelle).]

167. Dr. Labelle testified that though the beta substitution removed the toxicity issue, it "was one of the many things we could have tried. We tried many, many. We had many ideas. We got lucky [with the beta substitution]." [T. Tr., Feb. 23, 2009 P.M. 35:9-12, 17-21.]

168. The beta substitutions took place in late 1990. [T. Tr., Feb. 23, 2009 P.M. 35:15-16 (Labelle).]

169. The Merck chemists first substituted one, then two, methyls in the beta position. The chemists found that the dimethyl substitution resulted in a compound with no enzyme induction and a longer half-life. [T. Tr., Feb. 23, 2009 P.M. 36:5-10 (Labelle); TEX 3183.0035.]

170. Chemist and named inventor Dr. Yi B. Xiang took the resulting compound and added a carbon to the Q^1 side-chain. The result, L-705,254, had an even longer half-life and further reduced liver toxicity. [T. Tr., Feb. 23, 2009 P.M. 37:12-20 (Labelle); TEX 3183.0036.]

171. The chemists then bonded the two methyls in the beta position to make a cyclopropyl ring. Though the chemists made additional analogs (variations), they found that the cyclopropyl-containing compound, L-706,631, was the most potent. [T. Tr., Feb. 23, 2009 P.M. 39:5-18 (Labelle); TEX 3183.0037.]

172. L-706,631, re-named MK-476 in development, proved to be more potent than MK-679, and it had a longer half-life. It also did not cause liver toxicity. [T. Tr., February 23, 2009 P.M. 40:12-22; TEX 3183.0038.]

173. The chemists recommended that MK-476 be considered for development. [February 23, 2009, p.m., T. Tr. 40:23-41:7; TEX 3167.]

174. MK-476 ultimately was re-named montelukast, the active ingredient in Singulair® tablets. [T. Tr., Feb. 23, 2009 P.M. 40:7-9 (Labelle); Revised Final Pretrial Order, Stipulated Fact 68 ("Montelukast sodium, which is the active ingredient in the products sold under the tradename SINGULAIR®, was, during its development, also referred to by its compound number, L-706,631 or MK-0476.").]

C. Many Contributed to Merck's LTD_4 Antagonist Program

175. It took the Merck team over twelve years to develop a commercially successful LTD_4 antagonist.

176. At least 40 to 50 scientists contributed to the development of montelukast. [T. Tr., Feb. 23, 2009 P.M. 42:9-13 (Labelle); TEX 3183.0001.]

177. Merck chemists developed and tested approximately 1000 compounds over the course of Merck's LTD_4 antagonist program. [T. Tr., Feb. 23, 2009 P.M. 43:14-20 (Labelle).]

178. Approximately 229 of these compounds were developed and tested before the first tertiary alcohol-containing compound was made. [T. Tr., Feb. 23, 2009 P.M. 46:3-8 (Labelle); TEX 17, TEX 3137, TEX 3223.]

179. Approximately 335 compounds were made and tested between the synthesis of the first tertiary-containing compound and the synthesis of montelukast. [T. Tr., Feb. 23, 2009 P.M. 46:21-47:1 (Labelle).]

180. After montelukast was synthesized, the Merck chemists made and tested an additional 396 compounds. [T. Tr., Feb. 23, 2009 P.M. 47:2-4 (Labelle); *see also* T. Tr., Feb. 23, 2009 A.M. 83:4-7 (Young).]

181. Merck's backup program to montelukast lasted over two years. [T. Tr., Feb. 23, 2009 P.M. 43:11-13 (Labelle); *see also* T. Tr., Feb. 23, 2009 A.M. 83:4-7 (Dr. Young explained that even after montelukast was made, Merck continued to make and test many compounds).]

III. Claims 18-22 of the '473 Patent are Valid

182. Teva cannot sustain its high burden of demonstrating with clear and convincing evidence that claims 18-22 of the '473 patent are obvious.

183. Teva's obviousness analysis for claims 18-22 depends upon a combination of Young '89, U.S. Patent No. 5,104,882 ("the '882 patent"), and European Patent Application 0 318 093 ("EP '093"). [T. Tr., Feb. 24, 2009 A.M. 125:18-126:5.] European Patent Application 0 399 818 ("EP '818") is the foreign counterpart to the '882 patent and includes the same exemplar compounds. [TEX 0284.] EP '093 is an earlier-filed foreign counterpart to the '882 patent and includes only the first 96 exemplar compounds listed in EP '818 and the '882 patent. [TEX 0096.]

184. Dr. John G. Gleason, Merck's medicinal chemistry expert, reviewed Teva's obviousness arguments in light of the state of the art in leukotriene antagonist research at the time of the invention and came to the conclusion that the compounds claimed in claims 18-22 of the '473 patent would not have been obvious to a person of ordinary skill in the art at the time of the invention. [T. Tr., Feb. 25, 2009 A.M. 47:1-14, 108:8-15 (claims 18 and 19), 108:16-25 (claim 20), 109:1-6 (claims 21-22).]

A. Person of Ordinary Skill in the Art

185. Dr. George Lenz, Teva's expert witness on obviousness, does not meet Teva's own definition of one of ordinary skill in the art, as that term is defined in Teva's paragraph IV certification notice. [T. Tr., Feb. 24, 2009 A.M. 136:6-137:21 (Lenz); TEX 3003.0117.]

186. Teva's paragraph IV certification notice includes a definition of the level of skill in the art:

> The prior art demonstrates a reasonably high level of skill. One of ordinary skill in the art would possess substantial training in chemical and biological sciences with a Ph.D. or equivalent degree, training in the areas of synthetic organic chemistry, pharmacology or a related field, and experience working in research and development of leukotriene antagonists and leukotriene biosynthesis inhibitors. This person would have familiarity with the classes of leukotrienes, structure/function relationships of small molecule binding to the leukotriene receptors as well as standard assays in the art for determining in vivo activity as both leukotriene antagonists or leukotriene biosynthesis inhibitors. Such an individual would easily have understood the prior art references and have the capacity to draw inferences from them.

[TEX 3005.0006-0007.]

187. Teva reiterated this position as the level of skill in the art in its Supplemental Response to Merck's Interrogatory No. 11. [TEX 3246.0002-0003.]

188. Dr. Lenz testified that he does not have the "experience working in research and development of leukotriene antagonists" required by Teva's definition. [T. Tr., Feb. 24, 2009 A.M. 136:3-5, 137:15-20.]

189. After hiring Dr. Lenz to conduct Teva's obviousness analysis, Teva submitted a new definition of one of ordinary skill in the art in the Revised Final Pretrial Order. [Docket Entry No. 62 at 54.] This definition is inconsistent with Teva's Supplemental Response to Merck's Interrogatory No. 11 in that it omits any reference to the person of ordinary skill in the art having experience in the art of designing leukotriene antagonists:

> As of October 12, 1990, the hypothetical person having ordinary skill in the art of the '473 patent would possess a reasonably high level of skill. One having ordinary skill in the art would possess substantial training and experience in medicinal chemistry, experience or training in the chemical and biological sciences with a Ph.D. or equivalent degree in chemistry, experience or training in synthetic organic chemistry, and at least two years of experience in drug discovery, design, testing, and development. Such a person would have understood the prior art references and have the capacity to draw inferences from them, individually and overall, in designing LTD4 antagonists.
>
> [*Id.*]

190. Dr. Gleason testified that one of skill in the art should have several years of experience working in the field of leukotriene antagonists. [T. Tr., Feb. 25, 2009 A.M. 93:13-24.]

191. Dr. Gleason's observation is in line with Merck's definition of obviousness, as submitted to the Court in the Revised Final Pretrial Order:

> One of ordinary skill in the art should be understood as someone with substantial training in the chemical and biological sciences with an advanced degree in chemistry, training in the areas of synthetic organic chemistry and medicinal chemistry, and substantial experience working in the research and development of leukotriene antagonists.
>
> [Docket Entry No. 62 at 24.]

192. Dr. Gleason, Merck's medicinal chemistry expert, received a bachelor's degree in Chemistry from Loyola and a PhD in Chemistry from McGill University. [T. Tr., Feb. 25, 2009 A.M. 41:10-13 (Gleason).] Dr. Gleason then completed a year-long post doctoral fellowship at the Swiss Federal Institute of Technology in Zurich before joining Smith Kline & French in 1971 as a medicinal chemist. [*Id.* at 41:13-16.] Dr. Gleason worked at Smith Kline & French (later known as GlaxoSmithKline) for about 37 years before retiring. [*Id.* at 17-20.] During his employment, Dr. Gleason ascended to various levels of management, including Vice President and Director of Medicinal Chemistry for United States operations (just before Smith Kline & French's merger with Glaxo) and Vice President of Chemistry for the Cardiovascular Urogenital and Oncology Center of Excellence for Drug Discovery after the merger. [*Id.* at 42:3-10.]

193. Dr. Gleason was involved in Smith Kline & French's LTD_4 antagonist program since before the discovery of the leukotrienes. [T. Tr., Feb. 25, 2009 A.M. 42:17-21 (Gleason).] Smith Kline & French had a research program in asthma that sparked interest in SRS-A that eventually led to a program specifically focused on leukotrienes – this followed Samuelsson and Corey's discovery of the structure of LTD_4. [*Id.* at 42:21-43:3.] Dr. Gleason was one of the originators of that program and led the chemistry side of that program as either Program Leader or Co-Leader for its entire duration. [*Id.* at 43:3-8.] This effort lasted from late-1979/early-1980 through the early 1990s, when Smith Kline & French ultimately decided to in-license a leukotriene antagonist from another company and the focus at Smith Kline & French shifted from drug discovery to drug development. [*Id.* at 43:9-19.]

194. Similar to the experience at Merck described by Dr. Labelle, the work force dedicated to the discovery of a safe and effective leukotriene antagonist at Smith Kline & French varied over time from about four or five chemists in the beginning to about 15 chemists at the program's peak. [T. Tr., Feb. 25, 2009 A.M. 43:20-24 (Gleason).] Also similar to the experience at Merck, the corresponding biology work force started off smaller and grew over time as well. [*Id.* at 43:25-44:1.]

195. The leukotriene antagonist program at Smith Kline & French "was a major program. It was one of the largest resourced program[s] at the time at SK&F." [T. Tr., Feb. 25, 2009 A.M. 44:4-5 (Gleason).]

196. The first thing that Dr. Lenz did in preparing for this case was to look up the structure of montelukast. [T. Tr., Feb. 24, 2009 A.M. 139:4-13 (Lenz).]

197. The members of the Smith Kline & French program published their findings extensively, and several of the Smith Kline & French publications, including articles authored by Dr. Gleason, were relied on by Dr. Lenz to make himself familiar with the state-of-the-art in leukotriene antagonist research as of 1990 to 1991. [T. Tr., Feb. 25, 2009 A.M. 45:18-21 (Gleason).]

198. In trying to educate himself in the field of leukotriene antagonists, Dr. Lenz read only about 50 articles before rendering his opinion. [T. Tr., Feb. 24, 2009 A.M. 138:10-15 (Lenz).] Some of those 50 articles were published after the 1990 to 1991 timeframe. [*Id.* at 138:16-139:3.]

199. Dr. Lenz agrees that one publication sets out the state of the art in 1990 fairly accurately. [T. Tr., Feb. 24, 2009 A.M. 140:17-23; 142:10-14 (Lenz).] That publication is a chapter titled "Leukotriene Receptors," appearing in *Comprehensive Medicinal Chemistry* and written by W. Kingsbury and others, including Merck's medicinal chemistry expert Dr. Gleason ("the Kingsbury publication"). [*Id.*; TEX 3131.]

200. Dr. Lenz did not attend any conferences or meetings related to leukotriene antagonists and did not speak to anyone who had, so Dr. Lenz is not privy to all the discussions at such meetings and conferences. [T. Tr., Feb. 24, 2009 A.M. 141:10-24 (Lenz).]

201. Dr. Gleason not only "attended quite a number of conferences," he was invited as a speaker to many of them as well. [T. Tr., Feb. 25, 2009 A.M. 45:22-46:1 (Gleason).]

202. For at least the last 14 months, Dr. Lenz has worked mostly as a consultant in litigations, not a medicinal chemist. [T. Tr., Feb. 25, 2009 18:19-25 (Lenz).] This, despite lacking any actual medicinal chemist experience in the leukotriene antagonist field.

203. Before Dr. Gleason's involvement in this case, he had never been involved in litigation before. [T. Tr., Feb. 25, 2009 A.M. 48:7-12 (Gleason).]

B. Teva's Obviousness Analysis

204. Teva has incorrectly defined the "problem" to be addressed in its obviousness analysis in terms of the solution addressed by the '473 patent. [Docket Entry No. 73 at 31 (Defendants' Pretrial Brief detailing Teva's obviousness analysis that begins "[t]he problem addressed by the '473 patent was to identify additional quinoline-based LTD_4-antagonists").]

205. A person of ordinary skill in the art at the time would have been motivated to examine a variety of compound structures, not just quinoline-based antagonists. Even if a person of ordinary skill focused on quinoline-based antagonists, that person would have been motivated to look to the entire available quinoline-based art, not just Merck compounds.

206. By April of 1991, one of ordinary skill in the art would have been aware of at least ten compounds in the area of leukotriene antagonists that were in pre-clinical or clinical evaluations. [T. Tr., Feb. 24, 2009 P.M. 13:24-14:11; 33:17-34:3.] There were also biological assay data available for each of those ten compounds. [T. Tr.,

Feb. 24, 2009 P.M. 14:12-14, 14:17-18, 34:1-3.] And five of those ten compounds are quinoline-based. [T. Tr., Feb. 24, 2009 A.M. 34:4-5; 42:14-20 (the Revlon, Rorer, Wyeth, Leo, and Merck compounds are all quinoline-based).]

207. Those compounds available to a person of ordinary skill in the art that were in pre-clinical or clinical trials in 1991 included:

a. LY203647, manufactured by Eli Lilly & Co. [T. Tr., Feb. 24, 2009 A.M. 144:6-15; TEX 3202.0002];

b. RG-12525, manufactured by Rhone-Poulenc Rorer [T. Tr., Feb. 24, 2009 A.M. 144:16-145:5; TEX 3131.0017; TEX 3203.0002];

c. WY-48252, manufactured by Wyeth Pharmaceuticals [T. Tr., Feb. 24, 2009 A.M. 145:10-22; TEX 3131.0017-18; TEX 3203.0002];

d. SR-2640, manufactured by Leo Pharmaceuticals [T. Tr., Feb. 24, 2009 A.M. 146:17-23, 147:3-18; TEX 3131.0018; TEX 3203.0002];

e. RS-411, manufactured by Ono Pharmaceutical [T. Tr., Feb. 24, 2009 P.M. 4:23-5:1, 8:25-9:10; TEX 3131.0018; TEX 3203.0002];

f. ICI-204219, manufactured by Imperial Chemical Industries [T. Tr., Feb. 24, 2009 P.M. 9:11-15, 10:19-11:5; TEX 3131.0019; TEX 3203.0002];

g. SKF-104353, manufactured by Smith Kline & French [T. Tr., Feb. 24, 2009 P.M. 11:15-12:5; TEX 3131.0016; TEX 3203.0002];

h. SKF-106203, manufactured by Smith Kline & French [T. Tr., Feb. 24, 2009 P.M. 12:6-12; TEX 3131.0016; TEX 3203.0002];

i. REV-5901, manufactured by Revlon [T. Tr., Feb. 24, 2009 P.M. 13:2-8; TEX 3131.0017]; and

j. L-660,711, manufactured by Merck. [T. Tr., Feb. 24, 2009 A.M. at 104:15-22; TEX 3131.0019, 0022; TEX 3203.0002 (identified as MK-571).]

208. Dr. Lenz testified that he would have been aware of these compounds and that the compounds exhibited desirable properties. [*See, e.g.*, T. Tr.,

Feb. 24, 2009 A.M. 146:9-16, 147:9-18; T. Tr., Feb. 24, 2009 P.M. at 34:24-25.] Dr. Lenz also testified that a person of ordinary skill in the art would look to this data because drug discovery is based on data. [T. Tr., Feb. 24, 2009 P.M. 35:1-4.] But Teva has offered no explanation as to why a person of ordinary skill in the art would not have chosen one of these actual compounds (that had been shown to be effective as a starting point) over Dr. Lenz's hypothetical lead structure, for which no clinical data was available.

209. At the time of the invention, there would have been no way to know which of the ten compounds in preclinical or clinical evaluations would eventually lead to a viable commercial compound. [T. Tr., Feb. 24, 2009 P.M. 36:18-36:23 (Lenz); T. Tr., Feb. 25, 2009 A.M. 64:5-9, 81:23-82:1 ("At that stage, they all look very good and it would be just simple guesswork.") (Gleason).]

210. There would have been "[n]o obvious reason" to begin with a Merck compound as a lead compound. [T. Tr., Feb. 25, 2009 A.M. at 81:23-82:7 (noting that the Merck compound disclosed in Kingsbury failed in clinical trials) (Gleason).]

211. Dr. Lenz testified that, to his knowledge, no other "active" compounds existed for which there was a model. [T. Tr., Feb. 24, 2009 P.M. 36:23-37:4 (Lenz).] But a paper written by Hisao Nikai and others, titled "New Potent Antagonists of Leukotrienes C_4 and D_4. 1. Synthesis and Structure –Activity Relationships," specifically discusses the structure-activity relationships for the Ono compound RS-411, a compound that Dr. Lenz admits was known to be "very potent" and was being tested in man. [*Id.* at 38:18-39:25.]

212. There is no biological assay data available for Dr. Lenz's generic lead structure "[s]ince this [structure] is not an actual compound." [T. Tr., Feb. 24, 2009 P.M. at 14:15-20 (Lenz); *see also id.* at 40:13-17.]

213. In 1991, a person of ordinary skill in the art also would not have had access to biological assay data with respect to compound 97 of the '882 patent. [T. Tr., Feb. 24, 2009 P.M. 15:3-9, 40:18-20 (Lenz).]

214. Because several companies were entering preclinical evaluations or clinical trials with potentially marketable leukotriene antagonists, including with quinoline-based compounds, in the 1990 to 1991 timeframe, Merck's patents did not stifle the efforts of in this area. [*See* TEX 3131.0016-18; TEX 3203.0002.]

C. The Entirety of Teva's Obviousness Analysis is Conducted Without the Benefit of Data

215. Dr. Lenz concedes that the way that one generates a new compound is to make a new compound, test it, and see what happens. [T. Tr., Feb. 24, 2009 P.M. 69:10-13 (Lenz).]

216. But Dr. Lenz did not take any data into account in the generation of his intermediate structures; he makes all of the changes to get from his lead compound structure to montelukast without the benefit of any assay data. [T. Tr., Feb. 24, 2009 P.M. 69:6-9, 14-15 (Lenz).]

217. Dr. Lenz admitted that his analysis results in at least eleven distinct steps from L-660,711 to Dr. Lenz's generic lead compound structure to compound 97 to montelukast, all of which is accomplished without the benefit or support of any biological data:

<u>From L-660,711 to Dr. Lenz's generic lead compound structure</u>

a. Added a phenyl group to the Q^2 side chain [T. Tr., Feb. 25, 2009 A.M. 9:2-5, 9-14]

b. Added a substituent "X" to the phenyl ring on the Q^2 side chain and chose where to attach the "X" substituent (ortho, meta, or para positions possible) [T. Tr., Feb. 25, 2009 A.M. 9:15-22]

c. Replaced the sulfur atom of one of the two side chains with a carbon and chose to do so in the Q^2 side chain [T. Tr., Feb. 25, 2009 A.M. 10:8-10, 12:21-13:7, 13:12-19]

<u>From Dr. Lenz's generic lead compound structure to compound 97</u>

d. Chose a dimethyl amide for the "X" position of Dr. Lenz's generic lead compounds structure [T. Tr., Feb. 25, 2009 A.M. 15:7-13]

<u>From compound 97 to montelukast</u>

e. Chose to modify compound 97 by replacing the dimethyl amide, even though chose dimethyl amide in the first place because L-660,711 showed it worked well [T. Tr., Feb. 25, 2009 A.M. 15:11-20]

f. Chose an alcohol to replace the dimethyl amide and then chose tertiary alcohols from among at least three different types of alcohols [T. Tr., Feb. 25, 2009 A.M. 16:18-25]

g. Chose to length by a single carbon (as opposed to shorten or lengthen by more than one carbon) the Q^1 side chain (but not experiment with the length of the Q^2 side chain) [T. Tr., Feb. 25, 2009 A.M. 17:1-7]

h. Chose to add a group to the Q^1 side chain [T. Tr., Feb. 25, 2009 A.M. 8-10]

i. Chose what position (alpha or beta) to add the group and chose to add two methyl groups to that position [T. Tr., Feb. 25, 2009 A.M. 17:8-16, 17:23-18:1]

j. Convert those two methyl groups to a cyclopropyl group [T. Tr., Feb. 25, 2009 A.M. 18:2-7.]

k. Resolve the racemate. [T. Tr., Feb. 25, 2009 A.M. 18:9-14.]

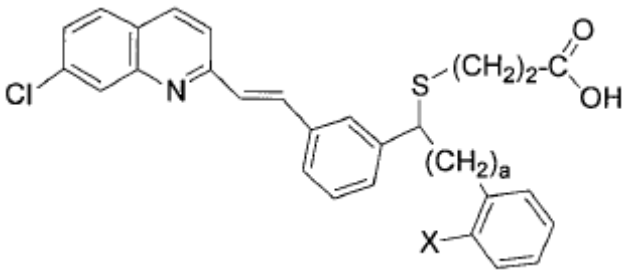
218. Dr. Lenz undergoes this analysis, in which he is at least eleven steps removed from the closest compound he can find with data, despite stating in his expert report that "the compound synthesized will be evaluated in biological assays and the results are a factor in designing the next set of analogs." [T. Tr., Feb. 25, 2009 A.M. 18:15-18.]

D. Teva Chose A Generic Lead Structure as the Starting Point for Its Obviousness Analysis

219. Teva elected to base its obviousness analysis on the initial selection of a lead compound structure. [*See* Docket Entry No. 73 at 31-34 (Defendants' Pretrial Brief); Docket Entry No. 62 at 63-65 (Revised Final Pretrial Order).]

220. MSD's Interrogatory No. 12 requests that Teva "[i]dentify the compound (or compounds if there is more than one) that as of October 20, 1990, a person of ordinary skill in the art would have chosen to modify in order to arrive at an LTD_4-antagonist for use in a commercial pharmaceutical formulation." [TEX 3243.0003.] MSD's Interrogatory No. 13 asks the same question with respect to the time period as of August 8, 1991. [*Id.*]

221. Following Magistrate Judge Hughes' August 27, 2008 Order that Teva "supplement the responses to Interrogatories 12 and 13 to include an identification of the lead compounds as of October 12, 1990, and of August 8, 1991, respectively, that a person of ordinary skill in the art would have chosen to modify in order to arrive at an LTD_4-antagonist for use in a commercial pharmaceutical formulation," [Docket Entry No. 30] Teva supplemented its responses to MSD's Interrogatories Nos. 12 and 13 and identified the following generic lead structure:



[Docket Entry No. 84, Exh. F at 2-4.]

E. Teva's Analysis Uses Hindsight and Ignores the Possible Lead Compounds

222. Dr. Gleason testified that Dr. Lenz, in arriving at his generic lead compound structure and lead compound, "makes a number of steps that are not supported by any data and that are not really supported by the model or . . . what would have been known about the SAR [structure-activity relationships] of these types of compounds." [T. Tr., Feb. 25, 2009 A.M. 80:19-25.]

223. Dr. Lenz testified that he applied four filters to come up with his lead compound structure. [T. Tr., Feb. 24, 2009 P.M. 46:3-5, 49:5-7.] Dr. Lenz also claims that these four filters led him to four compounds when he applied them to the '882 patent: compounds 97, 99, 393, and 394 of the '882 patent. [T. Tr., Feb. 24, 2009 P.M. 46:6-13; 54:20-21.]

224. Dr. Lenz suggested during his trial testimony that his analysis really started at a prior Merck compound, L-660,711, [T. Tr., Feb. 24, 2009 P.M. 35:24-36:3], then progressed through his generic lead compound structure before arriving at compound 97, which he then modified to arrive at montelukast.

225. Dr. Lenz also testified that compound 97 would have been particularly preferred because of the dimethyl amide at the "X" position of his generic lead structure. [T. Tr., Feb. 24, 2009 A.M. 128:21-129:9.]

226. When asked whether he had looked at the '882 patent to see if there were any other compounds that satisfied his filters, Dr. Lenz testified that he "went through [the '882 patent] several times and those were the four [he] found." [T. Tr., Feb. 24, 2009 P.M. 46:14-17.]

227. Dr. Lenz ignored that four other compounds – compounds 402, 409, 410, and 420 of the '882 patent – all satisfy his four filters as well, even when the preferred and more restrictive criteria that "X" be a dimethyl amide is applied. [T. Tr., Feb. 24, 2009 P.M. 48:11-13, 49:16-18, 49:22-50:3, 50:14-16.] Applying the same filters that allow Dr. Lenz to arrive at compounds 99, 393, and 394 of the '882 patent – where "X" can be any amide – two additional compounds, compounds 398 and 401 of the '882 patent, also satisfy Dr. Lenz's four filters. [TEX 0038 at col. 131-132.]

228. Dr. Lenz's filters say nothing about the position of "X" on the phenyl ring of the Q^2 side chain of Dr. Lenz's generic lead structure. [T. Tr., Feb. 24, 2009 P.M. 56:6-12 (Lenz).] "X" could occupy any one of three positions on the phenyl ring (ortho, or the position directly next to the carbon chain; meta, which would be one carbon removed from the carbon chain; or para, which would be directly opposite the carbon chain) on the phenyl ring. [T. Tr., Feb. 25, 2009 A.M. 92:13-16 (Lenz).]

229. Dr. Lenz's filters say nothing about having only one side chain with a sulfur atom. [T. Tr., Feb. 24, 2009 P.M. 49:8-18 (Lenz).]

230. Dr. Lenz's filters say nothing about having chlorine substitution on the phenyl ring of the Q^2 side chain. [T. Tr., Feb. 24, 2009 P.M. 56:1-2 (Lenz).]

231. Of the additional compounds that meet Dr. Lenz's filters but were not considered by Dr. Lenz during his obviousness analysis, compounds 409 and 420 do not include a chlorine substitution on the phenyl ring of the Q^2 side chain. [TEX 0038 at col. 130-132; T. Tr., Feb. 24, 2009 P.M. 56:20-22.]

232. Dr. Lenz cherry-picked, with the benefit of hindsight, those compounds with structures that he perceived to require the fewest modifications to get to montelukast. Of the ten compounds that actually satisfy Dr. Lenz's general four filters, the six that he ignored (compounds 398, 401, 402, 409, 410, and 420) all require additional modifications to result in montelukast. Of the five compounds that actually satisfy Dr. Lenz's four filters with the more preferred substitution of a dimethyl amide, the four compounds that he ignored (compounds 402, 409, 410, and 420) all require more modifications than the one he did choose – compound 97 – to result in montelukast. [*See* FF 222-227.]

233. Dr. Lenz read Teva's paragraph IV certification notice and understood that it was an obviousness analysis that Teva submitted to Merck. [T. Tr., Feb. 24, 2009 P.M. 50:17-23 (Lenz).] That notice specifically calls out 17 compounds from the '882 patent in its obviousness analysis. [*Id.* at 51:1-4, 52:14-23.]

234. Compound 97 is not mentioned in Teva's paragraph IV certification notice. [TEX 3005.0007-10.]

235. Compounds 99, 393, and 394 are also not mentioned in Teva's paragraph IV certification notice. [TEX 3005.0007-10.]

236. None of the 17 compounds listed in Teva's paragraph IV certification notice pass Dr. Lenz's four filters. [T. Tr., Feb. 24, 2009 P.M. 52:14-53:6 (Lenz).]

237. Dr. Lenz started his obviousness analysis with the structure of montelukast already known; he ignored more complicated compounds that met his own criteria; and, as shown below, he ignored multiple prior art references that would have discouraged many of the modifications he made to his generic lead compound structure.

F. The Young '89 Model

238. Merck's expert Dr. William L. Jorgensen analyzed the Young '89 model (described in detail below) to determine whether the model has any usefulness in the design of chemical compounds. [T. Tr., Feb. 26, 2009 23:22-24:2.] He determined

that it did not. [T. Tr., Feb. 26, 2009 26:4-5 ("[T]here really is no practical value to this that I can see.").]

239. Dr. Jorgensen received an undergraduate degree in chemistry from Princeton University and a Ph.D. in chemistry and chemical physics from Harvard University. [T. Tr., Feb. 26, 2009 22:3-17.] He also undertook five years of graduate and post-doctrinal studies under E. J. Corey at Harvard, where he was one of roughly ten graduate students. [*Id.*] Dr. Jorgensen is presently a professor at Yale University, Department of Chemistry, and engages in a wide range of chemical endeavors. [*Id.* at 20:11-21.] Dr. Jorgensen is "probably one of the most famous chemists in the world" and has received numerous awards for his achievements. [*Id.* at 22:20-23:4.] A major activity of Dr. Jorgensen's laboratory is computer-aided drug design and synthesis, and Dr. Jorgensen works extensively with very detailed models that recreate target structures in atomic detail. [*Id.* at 20:21-23, 24:12-21.] Dr. Jorgensen also has a good historical perspective on the evolution of drug discovery, including the state of the art in 1990. [*Id.* at 36:4-5, 36:8-12.]

1. Presentation of the Young '89 Model to the Public

240. Dr. Young presented a conceptualized model of the LTD_4 receptor at a conference in 1989 in Taipei ("the Young '89 model"). [T. Tr., Feb. 23, 2009 A.M. 71:22-72:3, 73:12-20; TEX 3283.] Dr. Young testified that the information used to develop the Young '89 model "sort of crystallized into a cartoon-like model in . . . late '87, '88, essentially for the Taipei meeting." [T. Tr., Feb. 23, 2009 A.M. 82:18-23.]

241. Dr. Young also published a paper following the Taipei conference, summarizing his presentation. [T. Tr., Feb. 23, 2009 A.M. 82:18-23.] That paper has been referred to in this case as Young '89. [TEX 3283.]

242. The "model" presented at the Taipei conference and included in Young '89 was Dr. Young's attempt to bring together in a pictorial representation information already known in the publicly available literature from Merck's own work and from other's work. [T. Tr., Feb. 23, 2009 A.M. 73:12-20 (Young).] Dr. Young intended his Taipei presentation and 1989 paper to be a review of the research conducted in the field up to that time. [T. Tr., Feb. 23, 2009 A.M. 74:1.]

2. The Young '89 Model is Too Crude to Provide Guidance in the Development of an LTD_4 Antagonist

243. Dr. Jorgensen reviewed Young '89 to determine whether it would be useful in drug design and determined that it would not. [T. Tr., Feb. 26, 2009 26:4-5 ("there's really no practical value to this that I can see").] Dr. Jorgensen testified that this is because in the Young '89 model "there is no detail as far as [he is] concerned that could allow one to progress in a sensible fashion towards a drug." [*Id.* at 26:8-11.]

244. Young '89 does not address things like steric requirements, the shape of the receptor, the requisite polarity to bind with the receptor, and the directionality of potential hydrogen bonds. [T. Tr., Feb. 25, 2009 A.M. 107:11-15, 107:23-108:4 (Gleason).] "Young 89 is very broad and very non-informative." [*Id.* at 107:14-15.]

245. Dr. Xiang testified that the Young '89 model is "really not an LTD_4 receptor model. It has nothing to do with LTD_4 receptor model. It is just a hypothesis to see how the compound or the ligand might bind to the receptor. . . it is not any model in a sense, in the common sense, the way a medicinal chemist is talking about a model." [Xiang Dep. Tr. 57:24-58:2; 58:13-16.]

246. Dr. Guay characterized the Young '89 model as "a very gross cartoon. If this is meant to represent a complex three-dimensional structure or protein, it is totally useless to me." [Guay Dep. Tr. 87:10-13.]

247. Dr. Labelle never used the Young '89 model in designing backup compounds to MK-571. When asked why, Dr. Labelle responded: "It doesn't really have any kind of value, as far as I am concerned. We're actually concerned with making a backup to MK-571, so we start with MK-571 and change the structure. Having a representation that is vague about what is needed is not something we use." [T. Tr., Feb. 23, 2009 P.M. 6:12-21.]

248. Dr. Leger testified that "anything can fit" in the Young '89 model. [Leger Dep. Tr. 134:2-4.]

249. Dr. Robert Zamboni is a medicinal chemist who was involved in the Merck leukotriene antagonist project. [Zamboni Dep. Tr. 8:14-9:17.] He echoed Dr. Leger's statement: "Anything in this patent, anything in competitors' patents, just about everything that's a leukotriene antagonist fits in that model, can be made to fit in that model." [*Id.* at 56:8-11.]

250. Dr. Zamboni testified that "[a]bout a million compounds fit [the Young '89] model. It's a hole. . .. It's a hole with some very abstract points. I can fit the proverbial kitchen sink in that model and claim it will be an LTD_4 antagonist. It doesn't tell me what to make. . .. This model was an abstraction. This model wasn't something we used day-to-day to help us design leukotrienes." [Zamboni Dep. Tr. 44:3-21.]

251. Mr. Belley testified at his deposition that "[i]f you look at the model itself, it doesn't say anything about what you have in the middle here, how to connect those things together. So there are millions of way[s] to connect everything together, if not billions. So if you look at the compound[s] we have in our own sample collection and that are everywhere that chemists made around the world, th[ere] are probably a third of the compound[s] that all the chemists made that could fit the model." [Belley Dep. Tr. 65:5-14.]

252. Dr. Young testified that "many millions" of compounds could fit within the bounds of the conceptual receptor model. [T. Tr., Feb. 23, 2009 A.M. 76:2-7.]

253. Dr. Gleason similarly testified that "hundreds of thousands, millions" of compounds fit the Young '89 model. [T. Tr., Feb. 25, 2009 A.M. 66:1-4.]

254. And Dr. Jorgensen opined that there is potentially "an infinity of molecules that can fit" the Young '89 model. [T. Tr., Feb. 26, 2009 26:20-21.]

255. Dr. Gleason testified that the Young '89 model would not provide any guidance as to distinguishing between any of the huge number of potential compounds that fit the model. [T. Tr., Feb. 25, 2009 A.M. 66:5-8.] Dr. Jorgensen agreed that the model "really doesn't help guide me in any way to decide which among that infinity of molecules that I would pursue." [T. Tr., Feb. 26, 2009 26:21-23.]

256. Dr. Guay explained that a chemist "could have ten thousand different molecules that have nothing to do with LTD_4 activity that could fit" the Young '89 model. [Guay Dep. Tr. 91:25-92:2.]

3. The Young '89 Model Does Not Suggest that An Alcohol Would Be Desirable as A Side Chain Substituent

257. Dr. Lenz admits that all of the 423 examples listed as substituents for the Q^2 position of the '882 patent would satisfy the criteria of the Young '89 model: at least one of the side chains include a substituent that is polar, non-ionizing, and a hydrogen bond acceptor. [T. Tr., Feb. 24, 2009 P.M. 63:4-15.] Dr. Lenz admits that this includes at least sulfonyls [*id.* at 58:1-10]; nitriles [*id.* at 58:16-22]; aldehydes [*id.* at 58:25-59:8]; trifluroacetyls [*id.* at 59:16]; ketones [*id.* at 59:18-25]; sulfoxides [*id.* at 60:18-61:2]; sulfides [*id.* at 61:6-14]; sulfonamides [*id.* at 61:20-62:1]; and tetrazoles. [*Id.* at 62:10-25; *id.* at 63:1-3.]

258. Dr. Gleason identified approximately 30 to 40 classes of substituents that would satisfy the criteria of the Young '89 model. [T. Tr., Feb. 25, 2009 A.M. at 71:2-7.] Each of those classes includes numerous specific substituents that would satisfy the criteria. [*Id.* at 72:1-4.]

259. The Young '89 model does not suggest that any of these groups would be any more desirable than the next – "this is the big limitation of the Young model." [T. Tr., Feb. 25, 2009 A.M. 72:5-9 (Gleason).] The Young '89 model "doesn't tell you anything about the size of the pocket, it doesn't tell you whether its small or large, so it doesn't [give] you [a] steric guide. It doesn't tell you what level of polarity you need." [*Id.* at 72:23-73:2.] In addition, directionality is very important to hydrogen binding, and "[t]he model doesn't tell you how the hetero (sic) atom in your polar, hydrogen bond acceptor . . . should point, what its orientation should be." [*Id.* at 73:10-25.]

260. There is a tremendous range of properties and shapes and sizes in the groups that could fit the Young '89 model, and the model does not identify which properties or shapes or sizes would be desirable. [T. Tr., Feb. 25, 2009 A.M. 74:1-15.]

261. More importantly, nothing in Young '89 suggests the use of a tertiary alcohol in the Q^2 position. [Belley Dep. Tr. 154:18-155:7.]

262. Dr. Jorgensen testified that "[i]t's not possible . . . from [his] perspective to see how you go from [the Young receptor] model to specifically coming up with a tertiary alcohol." [T. Tr., Feb. 25, 2009 A.M. 37:6-8.]

263. Indeed, as inventor Michel Belley testified, the model disclosed in the Young publications "doesn't suggest anything . . . there is nowhere in the paper where they suggest testing alcohol. There is nowhere in the paper that suggests that an alcohol might be good there." [Belley Dep. Tr. 154:4-155:7].

264. Even Dr. Lenz agrees that the Young '89 model would not direct one of ordinary skill in the art to pick a specific group. [T. Tr., Feb. 24, 2009 P.M. 64:5-7.]

4. The Young '89 Model Does Not Teach that A Primary Alcohol Would Be Interchangeable with Either A Secondary or A Tertiary Alcohol

265. Young '89 does not mention alcohols, [FF 254] much less that a primary alcohol would be interchangeable with a secondary or tertiary alcohol. In fact, each of these groups have specific properties and characteristics that suggest they would not be interchangeable in a chemical compound.

266. Dr. Young testified that a tertiary alcohol is not interchangeable with a primary alcohol. [T. Tr., Feb. 23, 2009 A.M. 83:8-14.]

267. Dr. Jorgensen testified that "[t]here isn't any interchangeability . . . between primary, secondary, and tertiary alcohols. They're very different beasts." [T. Tr., Feb. 26, 2009 30:2-4.]

268. Dr. Gleason testified that it is well known in organic chemistry that a tertiary alcohol is much more reactive than a primary alcohol and that a benzylic alcohol is much more reactive that an ordinary alcohol. [T. Tr., Feb. 25, 2009 A.M. 49:25-50:50.] Dr. Jorgensen agreed with this analysis: "Tertiary alcohols, particularly benzylic or allylic, are unstable and are expected to decompose in even mildly acidic (sic) conditions. So it is very unusual to see a tertiary alcohol on a drug." [T. Tr., Feb. 26, 2009 29:20-23.]

269. Dr. Zamboni also testified that tertiary alcohols are less stable than primary alcohols in the presence of acids. [Zamboni Dep. Tr. 45:14-15.]

270. The size of a potential antagonist is an important consideration in drug development. If chemists make a compound too large, it will not fit in the receptor site. [T. Tr., February 23, 2009 A.M. 84:16-23.]

271. Dr. Young testified that during the 1988-1989 time frame the available evidence suggested that a larger, bulkier group would be more problematic. [T. Tr. February 23, 2009, A.M. 86:1-4.]

272. Tertiary alcohols are much larger than primary or secondary alcohols. [T. Tr., Feb. 25, 2009 A.M. 77:19-22, 78:7-14.] A tertiary alcohol is at least three times the size of a primary alcohol and about twice the size of a secondary alcohol. [*Id.*]

273. Tertiary alcohols also differ from primary alcohols in that tertiary alcohols are less polar that primary alcohols. [T. Tr., Feb. 25, 2009 A.M. 76:7-8, 78:3-6.]

274. Dr. Gleason also testified that he would expect that tertiary alcohols would differ from primary alcohols in their ability to hydrogen bond, especially because of interactions with the extra methyl groups on a tertiary alcohol. [T. Tr., Feb. 25, 2009 A.M. 76:5-77:9.]

5. The Young '89 Model Does Not Suggest that A Tertiary Alcohol Would Be Interchangeable with A Dimethyl Amide

275. From just the information in the Young '89 model, it is unclear whether a tertiary alcohol could even be used to replace a dimethyl amide. Although the two substituents are moderately similar in size, with the tertiary alcohol being slightly smaller on a gross scale, tertiary alcohols and dimethyl amides have different shapes, especially in the area where you would expect hydrogen binding to occur. [T. Tr., Feb. 23, 2009 A.M. 118:14-119:2.] And Dr. Young testified that "what is important is the size relative to the binding point and that's very important in terms of how far away that bulk is, not the gross overall bulk." [*Id.*] Because the Young '89 model does not specify the size or orientation of the pocket in which the tertiary alcohol would have to fit, it is unclear from the model whether a compound containing a tertiary alcohol would be able to bind to the receptor.

276. Dr. Jorgensen testified that the Young '89 model does not teach anything about the interchangeability of a dimethyl amide and a tertiary alcohol. [T. Tr., Feb. 26, 2009 29:2-4.]

277. A tertiary alcohol is less polar than an amide. [T. Tr., February 23, 2009 A.M. 80:3-6.]

278. When Mr. Belley suggested to Dr. Young that a tertiary alcohol be supplemented in place of an amide, Dr. Young told Mr. Belley that "he was wasting his

time. It was much too lipophilic an element." Dr. Young did not think that the resulting molecule would be potent. [T. Tr., Feb. 23, 2009 A.M. 79:15-80:2.]

279. Dr. Young believed that a hydrophilic element was needed to have an effective LTD_4 antagonist. [TEX 3283.0002.] Hydrophilic means "water-liking." As Dr. Young testified, "these alkyl groups on the tertiary alcohol are generally water-hating." [T. Tr., February 23, 2009 A.M. 80:11-17.]

6. The Young '89 Model Does Not Suggest that the Q^1 Side Chain Must Terminate in a Carboxylic Acid

280. Dr. Lenz admits that "Young 89 doesn't talk about Q^1 and Q^2." [T. Tr., Feb. 24, 2009 P.M. 18:15-17.]

281. Dr. Lenz also admitted that "Young 89 doesn't tell you whether Q^1 should be the acid and Q^2 should be something else." [T. Tr., Feb. 24, 2009 P.M. 19:8-11; *see also id.* at 28:20-24; 30:12-16.]

G. The Filters Teva Used to Arrive at its Lead Compound Structure are Flawed

1. Ethenyl Linker

282. Despite Teva's representations, Young '89 only suggests that the lipophilic pocket of the LTD_4 receptor requires a "generally extended planar conformation." [TEX 3282.0002; T. Tr., Feb. 25, 2009 A.M. 66:25-67:9 (Gleason).] This does not require extended conjugation as suggested by Dr. Lenz's obviousness analysis. Therefore, there is no reason to believe that the linker group connecting the central phenyl ring and the quinoline must contain a double bond (also known as an olefinic linker or an ethenyl linker). [T. Tr., Feb. 25, 2009 A.M. 66:9-17, 68:12-13 ("there's no requirement in the model for the double bond") (Gleason).]

283. In fact, Dr. Gleason testified that a linker group with a single bond may actually give you a flatter, more planar compound. [T. Tr., Feb. 25, 2009 A.M. 68:14-22.] This is because the double bond actually imposes a 20 to 30 degree tilt between the central phenyl ring and the quinoline tail, [T. Tr., Feb. 25, 2009 A.M. 67:16-23, 68:6-8], whereas the preferred conformation of a compound with a single bond linker will still be planar and will not have this imposed tilt. [T. Tr., Feb. 25, 2009 A.M. 68:14-22.]

284. This is consistent with the state of the art at the time of the invention. All four non-Merck quinoline-based leukotriene antagonists known to be in preclinical or clinical trials as of 1990 to 1991 used linkers with single bonds. [T. Tr., Feb. 25, 2009 A.M. 69:19-70:8, 84:25-85:5 (Gleason).]

285. Dr. Gleason's analysis is also consistent with the examples of the '882 patent, on which Dr. Lenz relies heavily for other aspects of his obviousness analysis. [T. Tr., Feb. 25, 2009 A.M. 85:5-8.] In the '882 patent, "the [single bond] ether linkage and to a lesser extent the [single bond] saturated ethyl linker are used extensively. And, in fact, the [double bond] unsaturated one [is] use[d] less." [*Id.*]

286. Dr. Gleason testified "that looking at all of the art, both the patent, what's known in the competitor's compounds and even the model, none of those suggest that you need a double bond." [T. Tr., Feb. 25, 2009 A.M. 85:8-11.]

2. Q^1 Must Have a Carboxylic Acid and Q^2 Must Have "X"

287. The second and third filters of Dr. Lenz's obviousness analysis require that the Q^1 side chain of his lead structure terminate in a carboxylic acid and the Q^2 side chain terminate in a polar, non-ionizing, hydrogen bond acceptor, respectively. According to Dr. Lenz's analysis in his rebuttal expert report, "[t]he teachings of Young '89 would have motivated a person of ordinary skill in the art to modify and focus on the [terminal] group of the Q^2 side chain" and "Young '89 teaches the preference for [a] dimethyl amide on the Q^2 chain, [and] the importance of keeping a carboxylic acid on the Q^1 chain." [T. Tr., Feb. 24, 2009 P.M. at 21:25-22:11.] Dr. Lenz's rebuttal expert report also states that "Dr. Gleason is mistaken" in "his opinion that the receptor model . . . does not indicate which of Q^1 or Q^2 [c]ould be modified to occupy the ionic pocket, nor indicates what the appropriate modifications would be." [*See id.* at 23:6-15.]

288. Dr. Lenz previously changed the opinion expressed in his expert report and stated that he would agree with Dr. Gleason that either the Q^1 or Q^2 side chain could be modified. [T. Tr., Feb. 24, 2009 P.M. 23:24-24:7.] Later in his deposition, Dr. Lenz changed his mind again, returning to his original position. [T. Tr., Feb. 24, 2009 P.M. 24:7-10 (Lenz).]

289. Dr. Lenz admits that "Young 89 doesn't talk about Q^1 and Q^2." [T. Tr., Feb. 24, 2009 P.M. 18:15-17.]

290. Dr. Lenz also admits that "Young 89 doesn't tell you whether Q1 should be the acid and Q^2 should be something else." [T. Tr., Feb. 24, 2009 P.M. 19:8-11; *see also id.* at 28:20-24; 30:12-16.]

291. Instead, Dr. Lenz testified that experiments conducted by Dr. E. J. Corey, published in 1981, would teach a person of ordinary skill in the art that the Q^1 side chain must contain an acid and that the Q^2 side chain could be something else. [T. Tr., Feb. 24, 2009 P.M. 9:8-11, 20:24-21:1, 24:10-13, 43:14-20; T. Tr., Feb. 25, 2009 A.M. 5:24-6:1.] Dr. Lenz testified that he had reached a conclusion regarding the interchangeability of the Q^1 and Q^2 side chains before drafting his initial expert report and that his first expert report listed everything on which he based his opinion. [T. Tr., Feb. 25, 2009 A.M. 5:12-6:7.] Dr. Lenz's initial expert report does not cite to the Corey '81 paper. [*Id.* at 6:8-9 (Lenz).]

292. The Corey paper is not cited in Young '89. [*Id.* at 24:25-25:13 (Lenz).] This led Dr. Lenz, during the second day of trial, to amend his expert report to reference Young '88 instead of Young '89. [T. Tr., Feb. 24, 2009 P.M. 31:18-32:3; 32:19-23.] Even then, what Dr. Lenz was citing was "not really Young 88, but, rather, it's an article that is cited in Young 88." [*Id.* at 33:9-16.]

293. Dr. Lenz attempted to rectify this by saying that data referenced in Young '89, which Dr. Lenz included in his expert report, was the data from the Corey paper. [*See* T. Tr., Feb. 25, 2009 A.M. 29:22-5, 30:23-31:5.] Dr. Lenz then changed back to his original opinion in his expert report, [*Id.* at 31:16-17], but the fact remains that neither Young '88 or Young '89 directly references the Corey work on which Dr. Lenz now says he is relying.

294. Further, the Corey work on which Dr. Lenz states he is referring is from a paper published in 1981. [T. Tr., Feb. 24, 2009 P.M. 5:24-6:1.] This is in direct contradiction to Dr. Lenz's suggestion elsewhere in his analysis that data that was even five years old in 1991 would be irrelevant. [*See* T. Tr., Feb. 25, 2009 A.M. 21:20-24.]

295. Dr. Lenz also stated that U.S. Patent No. 4,851,409 ("the 409 patent") tells you that the carboxylic acid must be in the Q^1 position. [T. Tr., Feb. 24, 2009 P.M. at 25:16-19.] But the '409 patent lists several examples of compounds in which the carboxylic acid is in the Q^2 position and a non-acid is in the Q^1 position. [T. Tr., Feb. 24, 2009 P.M. 27:6-12.] Therefore, and Dr. Lenz agrees, the '409 patent does not teach that the carboxylic acid must be at the Q^1 position. [*Id.* at 13-16.] Dr. Gleason confirmed that several examples from the '409 patent are inconsistent with Dr. Lenz's analysis. [T. Tr., Feb. 25, 2009 P.M. 29:6-15, 29:25-30:7.]

296. The '882 patent similarly includes several compounds with a Q^2 side chain that terminates in a carboxylic acid and a Q^1 side chain that terminates in a non-acid. [TEX 0038 at col. 15-20, 115-132.] Because the examples of the corresponding European patents EP '093 and EP '818 are subsumed with the '882 patent, [FF 183] both EP '093 and EP '818 also demonstrate the interchangeability of the Q^1 and Q^2 side chains in leukotriene antagonists.

297. The Q^1 and Q^2 side chains of the leukotriene antagonists at issue in this case are attached to the central phenyl ring by a common carbon atom, which allows the two side chains to rotate freely without requiring the entire molecule to change orientation. [T. Tr., Feb. 24, 2009 P.M. 43:21-25, 44:6-9 (Lenz); T. Tr., Feb. 25, 2009 A.M. 87:20-88:13 (Gleason).]

298. So "if you have the acid on Q^1 it can go into the correct pocket. If you have the acid on Q^2 it can still go into the same pocket, because that part of the molecule can rotate and just turn itself over. So based on that there is no way to say definitively which side chain, Q^1 or Q^2, needs to be the acid." [T. Tr., Feb. 25, 2009 A.M. 89:2-9 (Gleason).]

299. The Q^1 and Q^2 side chains of LTD_4, on the other hand, are directly attached to the corresponding central phenyl ring and cannot rotate freely. Therefore, the entire molecule must rotate in order to change the orientation of the Q^1 and Q^2 side chains. [T. Tr., Feb. 24, 2009 P.M. at 44:1-5 (Lenz).]

300. Corey's work focused on LTD_4 – the key discovery from this work was the structure of LTD_4, [T. Tr., Feb. 25, 2009 A.M. at 55:15-23, 56:4-10] – and Corey's conclusions regarding the interchangeability of the Q^1 and Q^2 side chains cannot be directly applied to the compounds at issue in this case. This argument is supported by the interchangeability of the Q^1 and Q^2 side chains seen in several of the later Merck patents, including the '409 patent, EP '093, EP '818, and the '882 patent.

301. Dr. Lenz chose to attach the "X" substituent of his generic lead compound structure to the ortho-position of the Q^2 phenyl ring but offered no rationale for doing so. The substituent could occupy any one of three different positions, and there is no data provided indicating which position would be preferred. [T. Tr., Feb. 25, 2009 A.M. at 92:13-20.]

4. Phenyl ring in Q^2 side chain

302. Dr. Lenz's fourth filter requires that the Q^2 side chain contain a phenyl ring, which he rationalizes by saying that the '882 patent includes such a structure. [T. Tr., Feb. 24, 2009 P.M. at 44:22-45:2.]

303. Dr. Lenz cannot point to any support anywhere suggesting that the inclusion of a phenyl ring in the Q^2 side chain would result in increased activity or other desirable properties. And Dr. Gleason testified that he could not see any reason to impose the inclusion of a phenyl ring in the Q^2 side chain as a filter for the lead compound structure, because there is no data or suggestion in the literature that doing so would be a good idea. [T. Tr., Feb. 25, 2009 A.M. at 91:21-92:2.]

H. Teva's Modifications of Its Lead Compound Structure are Also Flawed

304. Dr. Lenz's obviousness analysis relies upon a number of unsupported modifications of his generic lead compound structure in order to arrive at montelukast.

1. A Person of Ordinary Skill in the Art Would Not Choose A Tertiary Alcohol

305. Dr. Lenz testified that one of skill in the art would have most likely replaced the "X" of his generic lead structure with a dimethyl amide because the L-660,711 compound demonstrated that "the dimethyl amide had superior properties." [T. Tr., Feb. 24, 2009 A.M. at 128:21-129:3.] But after arriving at compound 97 as his most

preferred lead compound, Dr. Lenz replaces that very group with something else. [*Id.* at 131:14-17.]

306. Dr. Lenz chose to modify compound 97 by replacing the dimethyl amide, even though the reason he chose the dimethyl amide for the "X" position in the first place was because L-660,711 showed it worked well. [T. Tr., Feb. 25, 2009 A.M. at 15:11-16.]

307. Even accepting Dr. Lenz's suggestion that a person of ordinary skill in the art would have been motivated to replace the dimethyl amide with another polar, non-ionizing, hydrogen bond acceptor, [T. Tr., Feb. 24, 2009 P.M. at 57:4-12], several functional groups would be likely candidates for such a substitution. Dr. Lenz admits that all of the groups listed as substituents in the Q^2 position for all 423 examples of the '882 patent would satisfy the criteria of the Young '89 model that the substituent be polar, non-ionizing, and a hydrogen bond acceptor. [T. Tr., Feb. 24, 2009 P.M. at 63:4-15.] Dr. Lenz admits that this includes at least sulfonyls [*id.* at 58:1-10]; nitriles [*id.* at 58:16-22]; aldehydes [*id.* at 58:25-59:8]; trifluroacetyls [*id.* at 59:16]; ketones [*id.* at 59:18-25]; sulfoxides [*id.* at 60:18-61:2]; sulfides [*id.* at 61:6-14]; sulfonamides [*id.* at 61:20-62:1]; and tetrazoles [*id.* at 62:10-25; *id.* at 63:1-3].

308. Dr. Gleason identified approximately 30 to 40 classes of substituents that would satisfy the criteria of the Young '89 model for Dr. Lenz's "X" position. [T. Tr., Feb. 25, 2009 A.M. at 71:2-7.] Each of those classes also includes multiple groups that would satisfy the criteria. [*Id.* at 72:1-4.]

309. And the Young '89 model does not suggest which of those groups a person of ordinary skill in the art would chose as a possible replacement – "this is the big limitation of the Young model." [T. Tr., Feb. 25, 2009 A.M. at 72:5-9.] The Young '89 model "doesn't tell you anything about the size of the pocket, it doesn't tell you whether its small or large, so it doesn't [give] you [a] steric guide. It doesn't tell you what level of polarity you need." [*Id.* at 72:23-73:2.] In addition, directionality is very important to hydrogen binding, and "[t]he model doesn't tell you how the hetero (sic) atom in your polar, hydrogen bond acceptor . . . should point, what its orientation should be." [*Id.* at 73:10-25.]

310. There is a tremendous range of properties and shapes and sizes in the possible groups that could fit in the "X" position of Dr. Lenz's lead compound structure, and the Young '89 model does not identify which properties or shapes or sizes would be desirable. [T. Tr., Feb. 25, 2009 A.M. at 74:1-15.]

311. Dr. Jorgensen testified that "[i]t's not possible . . . from [his] perspective to see how you go from [the Young receptor] model to specifically coming up with a tertiary alcohol." [T. Tr., Feb. 25, 2009 A.M. 37:6-8.]

312. Dr. Lenz agrees that the Young '89 model would not direct one of ordinary skill in the art as to which of these groups to pick. [T. Tr., Feb. 24, 2009 P.M. 64:5-7.]

313. Dr. Lenz also agrees that when "look[ing] around at what had been shown to be compatible with side chains and had some activity" in order to find a suitable replacement for the "X" position, a person of ordinary skill in the art could look to publications with data if those publications describe compounds similar to the ones with which the person of ordinary skill was working. [T. Tr., Feb. 24, 2009 P.M. 64:8-19.]

314. The side chains of the L-660,711 compound came from the Smith Kline & French compounds. [T. Tr., Feb. 23, 2009 A.M. 66:22-67:2 (Young); T. Tr., Feb. 24, 2009 P.M. 64:22-65:1 (Lenz).] Accordingly, Dr. Lenz testified that it would be reasonable to look at data relating to the Smith Kline & French compounds when assessing the obviousness of certain changes to the side chains of his lead structure. [T. Tr., Feb. 24, 2009 P.M. 65:2-4.]

315. "Synthesis and LTD_4 Antagonist Activity of 2-Norleukotriene Analogues," written by Thomas W. Ku and others, including Dr. Gleason ("the Ku paper"), focuses on research done regarding the Smith Kline & French compounds and would have been available to one of ordinary skill in the art at the time of the invention. [TEX 3139; T. Tr., Feb. 24, 2009 P.M. 65:5-13 (Lenz) (this paper is referenced by the name "Coo" in the trial transcript).]

316. The Ku paper reports that when the Smith Kline & French scientists inserted an alcohol in what has been referenced in this litigation as the Q^2 side chain, the resulting compound showed decreased activity relative to a corresponding compound with a carboxylic acid at the Q^2 position. [T. Tr., Feb. 24, 2009 P.M. 65:20-66:7, 67:21-23, 68:19-22 (Lenz).] This information was repeated in the Kingsbury publication that Dr. Lenz agrees fairly sets out the state-of-the-art at the time of the invention. [*Id.* at 68:2-4.]

317. The Ku paper is the only publication that would have been available to a person having ordinary skill in the art that examines the potential use of an alcohol in the side chains of leukotriene antagonists, and it shows that inserting an alcohol decreased activity. Following the publication of the Ku paper, no intervening publications were released saying otherwise prior to 1990 or 1991. [T. Tr., Feb. 24, 2009 P.M. 68:5-7 (Lenz).]

318. Dr. Lenz tries to discount the Ku paper by stating that it was published in 1985. [T. Tr., Feb. 25, 2009 A.M. 21:20-24.] But contrasts sharply with Lenz's own use of the 1981 Corey paper as the basis for his obviousness analysis: (1) the Corey paper examined LTD_4 itself, not LTD_4 antagonists, the implications of which have already been examined, and (2) Dr. Lenz's argument that the Ku paper would be disregarded by a person of ordinary skill in the art because it was published in 1985 and the field "had progressed dramatically and moved very, very quickly" is incompatible

with Dr. Lenz's decision to base his entire obviousness analysis on a paper from 1981. Further, no intervening data disputed the results of the Ku paper, whereas several publications (including the very patents used in Dr. Lenz's obviousness analysis) suggest that Corey's conclusions regarding the interchangeability of the Q^1 and Q^2 side chains in LTD_4 do not translate to compounds where the side chains are allowed to rotate freely.

319. Young '89 does not suggest that a tertiary alcohol be substituted at the "X" position of the Q^2 side chain of Dr. Lenz's lead compound structure. [*See* T. Tr., Feb. 24, 2009 P.M. 64:5-7 (Dr. Lenz admits that Young '89 does not tell you what to chose for the "X" position).]

320. In fact, the first time that Dr. Gleason saw the structure of montelukast, he was "very" surprised to see a tertiary benzylic alcohol (a tertiary alcohol connected directly to a phenyl ring, as in the Q^2 side chain of montelukast). [T. Tr., Feb. 25, 2009 A.M. 48:13-15, 49:7-10.] Dr. Gleason was "very surprised that [there] would be that kind of functionality in a drug" because he would have expected such a functional group to be very reactive in the acidic environment of the stomach. [*Id.* at 49:10-14.]

i. A Primary Alcohol is Not Interchangeable With a Secondary or Tertiary Alcohol

321. Alcohols are known to be problematic when used in potential drugs. [T. Tr., Feb. 26, 2009 29:8-11 (Jorgensen).] Reviewing the related field of prostaglandin literature, it was well known that both secondary alcohols cause metabolism problems and that the use of tertiary alcohols results in unstable compounds that decompose in the acidic environment of the stomach. [*Id.* at 29:12-19.]

322. Dr. Jorgensen testified that "[t]here isn't any interchangeability . . . between primary, secondary, and tertiary alcohols. They're very different beasts." [T. Tr., Feb. 26, 2009 30:2-4.]

323. It is well known in organic chemistry that a tertiary alcohol is much more reactive than a primary alcohol and that an alcohol is much more reactive that an ordinary alcohol. [T. Tr., Feb. 25, 2009 A.M. 49:25-50:50 (Gleason).] "Tertiary alcohols, particularly benzylic or allylic, are unstable and are expected to decompose in even mildly acidic (sic) conditions. So it is very unusual to see a tertiary alcohol on a drug." [T. Tr., Feb. 26, 2009 29:20-23 (Jorgensen).]

324. Dr. Jorgensen, Merck's expert on the utility of the Young '89 model, testified that he would not consider including a tertiary alcohol in any of the compounds his group designs because they "try to conserve [their] resources and direct them into productive areas and [Dr. Jorgensen] feel[s] that dealing with certain functional groups including tertiary alcohols would be very risky." [T. Tr., Feb. 26, 2009 30:10-15.]

325. Dr. Zamboni also testified that tertiary alcohols are less stable than primary alcohols in the presence of acids. [Zamboni Dep. Tr. 45:14-15.]

326. The size of a potential antagonist is an important consideration in drug development. If chemists make a compound too large, it will not fit in the receptor site. [T. Tr., February 23, 2009 A.M. 84:16-23 (Young).]

327. Dr. Young testified that during the 1988-1989 time frame the available evidence suggested that a larger, bulkier group would be more problematic. [T. Tr. February 23, 2009, A.M. 86:1-4.]

328. Tertiary alcohols and secondary alcohols are much larger than primary alcohols. [T. Tr., Feb. 25, 2009 A.M. 77:19-22, 78:7-14 (Gleason).] A tertiary alcohol is at least three times the size of a primary alcohol, and a secondary alcohol is about twice the size of a primary alcohol. [*Id.*]

329. Tertiary alcohols also differ from primary alcohols in that tertiary alcohols are less polar that primary alcohols. [T. Tr., Feb. 25, 2009 A.M. 76:7-8, 78:3-6 (Gleason).]

330. Dr. Gleason also testified that he would expect that tertiary alcohols would differ from primary alcohols in their ability to hydrogen bond, especially because of interactions with the extra methyl groups on a tertiary alcohol. [T. Tr., Feb. 25, 2009 A.M. 76:5-77:9.]

ii. The Young '89 Model Does Not Suggest that A Tertiary Alcohol Is Interchangeable with a Dimethyl Amide

331. From just the information in the Young '89 model, it is unclear whether a tertiary alcohol could even be used to replace a dimethyl amide. Although the two substituents are moderately similar in size, with the tertiary alcohol being slightly smaller on a gross scale, tertiary alcohols and dimethyl amides have different shapes, especially in the area where you would expect hydrogen binding to occur. [T. Tr., Feb. 23, 2009 A.M. 118:14-119:2 (Young).] And Dr. Young testified that "what is important is the size relative to the binding point and that's very important in terms of how far away that bulk is, not the gross overall bulk." [*Id.*] Because the Young '89 model does not specify the size or orientation of the pocket in which the tertiary alcohol would have to fit, it is unclear from the model whether a compound containing a tertiary alcohol would be able to bind to the receptor.

332. Dr. Jorgensen testified that the Young '89 model does not teach anything about the interchangeability of a dimethyl amide and a tertiary alcohol. [T. Tr., Feb. 26, 2009 29:2-4.]

333. A tertiary alcohol is less polar than an amide. [T. Tr., February 23, 2009 A.M. 80:3-6 (Young).]

334. When Merck chemist Michel Belley suggested to Dr. Young that a tertiary alcohol be supplemented in place of an amide, Dr. Young told Belley that "he

was wasting his time. It was much too lipophilic an element." Dr. Young did not think that the resulting molecule would be potent. [T. Tr., February 23, 2009 A.M. 79:15-80:2 (Young).]

335. Dr. Young believed that a hydrophilic element was needed to have an effective LTD_4 antagonist. [TEX 3283.002.] Hydrophilic means "water-liking." As Dr. Young testified, "these alkyl groups on the tertiary alcohol are generally water-hating." [T. Tr., February 23, 2009 A.M. 80:11-17.]

2. Teva Offers No Rationale for Lengthening the Q^1 Side Chain

336. Dr. Lenz testified that one of the things a person of ordinary skill in the art would have done to his lead compound structure was to increase the length of the Q^1 side chain by one carbon by inserting an additional methyl group in the Q^1 chain. [T. Tr., Feb. 24, 2009 A.M. 129:18-20.]

337. The only rationale offered by Dr. Lenz as to this change is that experimenting with different lengths of side chains "is a standard operating procedure." [T. Tr., Feb. 24, 2009 A.M. 129:21-25.] But unlike the situation described by Dr. Labelle in his testimony, to which Dr. Lenz compares this analysis [*Id.*], Dr. Lenz was not making iterative changes to his structure and testing the results. [T. Tr., Feb. 24, 2009 P.M. 69:6-9, 14-15 (Lenz).]

338. Dr. Lenz offered no rationale as to why one of ordinary skill in the art would not have been equally motivated to experiment with the length of the Q^2 side chain instead of the Q^1 side chain, nor does Dr. Lenz even attempt to explain why one of skill in the art would not have tried decreasing the length of the side chains or increasing the length of those chains beyond three carbons.

339. Further, the evidence available to one of skill in the art at the time would have actually discouraged that person from increasing the length of the Q^1 side chain to three carbons.

340. The side chains of the L-660,711 compound came from the Smith Kline & French compounds. [T. Tr., Feb. 23, 2009 A.M. 66:22-67:2 (Young); T. Tr., Feb. 24, 2009 P.M. 64:22-65:1 (Lenz).] Accordingly, Dr. Lenz testified that it would be reasonable to look at data relating to the Smith Kline & French compounds when assessing the obviousness of certain changes to the side chains of his lead structure. [T. Tr., Feb. 24, 2009 P.M. at 65:2-4.]

341. "Synthesis and LTD_4-Antagonist Activity of Desamino-2-Nor-Leukotriene Analogues," written by Carl D. Perchonock and others, including Dr. Gleason ("the Perchonock paper"), focuses on research done regarding the Smith Kline & French compounds and would have been available to one of ordinary skill in the art at the time of the invention. [TEX 3143; T. Tr., Feb. 24, 2009 P.M. 70:3-10 (Lenz).]

342. When the Smith Kline & French scientists increased the length of the side chain corresponding to the Q^1 side chain to three carbons – "[j]ust like the side chain in [Dr. Lenz's] lead structure" – the intrinsic *contractile* activity of the compound doubled. [T. Tr., Feb. 24, 2009 P.M. 70:15-22, 71:13-15 (Lenz).] Dr. Lenz admitted that this is "not a desirable result" and "does not indicate that adding a carbon would do any good." [*Id.* at 71:19-20, 72:6-12.]

343. The Perchonock paper would have been the only literature available to a person of ordinary skill in the art in 1990 to 1991 with data regarding side chains similar to those used in Dr. Lenz's lead compound structure, and the Perchonock paper shows that extending the side chain length actually made those compounds more of an agonist, which is "taking you in completely the wrong direction." [T. Tr., Feb. 25, 2009 A.M. 95:20-25 (Gleason).]

344. Dr. Gleason testified that there would be no obvious reason to increase the length of the Q^1 side chain because several highly active compounds had side chains with two carbon chain lengths. [T. Tr., Feb. 25, 2009 A.M. 95:5-10.] Dr. Gleason also explained that you might explore changing the chain length as part of an ordinary medicinal chemistry program, but that in doing so, you would explore all parts of the compound, not just the Q^1 side chain. [*Id.* at 95:12-17.]

3. A Person of Ordinary Skill in the Art Would Not Have Been Concerned About Beta-Oxidation of the Q^1 Side Chain

345. Dr. Lenz testified that a person of ordinary skill in the art would have been concerned about beta-oxidation of the Q^1 side chain and that this concern would have led that person to add substituents to the beta-position of the Q^1 side chain to block the oxidation. [T. Tr., Feb. 24, 2009 AM. 130:1-16, 130:25-131:6]

346. As of the time of the invention, a person of ordinary skill in the art would not have been concerned about beta-oxidation in the Q^1 side chain.

347. The side chains of the L-660,711 compound came from the Smith Kline & French compounds. [T. Tr., Feb. 23, 2009 A.M. 66:22-67:2 (Young); T. Tr., Feb. 24, 2009 P.M. 64:22-65:1 (Lenz).] Accordingly, Dr. Lenz testified that it would be reasonable to look at data relating to the Smith Kline & French compounds when assessing the obviousness of certain changes to the side chains of his lead structure. [*Id.* at 65:2-4.]

348. "*In Vivo* Metabolism of the Leukotriene Receptor Antagonist, 5-(2-Dodecylphenyl)-4,6-Dithianonanedioic Acid (SK&F 102,081) in the Guinea Pig," written by John F. Newton and others, including Dr. Gleason ("the Newton paper"), focuses on research done regarding a Smith Kline & French compound and would have been available to one of ordinary skill in the art at the time of the invention. [TEX 3141; T. Tr., Feb. 24, 2009 P.M. 73:16-24 (Lenz).]

349. The Smith Kline & French compound examined in the Newton paper has a very similar side chain to that of the Q^1 side chain of the compound arrived at in Dr. Lenz's analysis. [T. Tr., Feb. 24, 2009 P.M. 74:18-20 (Lenz).] Despite following all paths of metabolism that this compound undergoes in the body of an animal, Dr. Lenz admits that the Newton paper does not show any beta-oxidation of the Q^1 side chain. [*Id.* at 74:25-75:3.]

350. During his redirect testimony, Dr. Lenz attempted to confuse this issue by suggesting that the Newton paper shows "omega followed by beta oxidation." [T. Tr., Feb. 24, 2009 P.M. 25:23-27:8.] This is especially misleading on Dr. Lenz's part. The evidence of omega-oxidation followed by beta-oxidation on which Dr. Lenz testified during his redirect examination occurs at the opposite end of the compound from the Q^1 side chain – at the lipophilic tail. [*Id.*] The Newton paper does not show any oxidation of any kind at the portion of the compound corresponding to the Q^1 side chain, and more importantly, Dr. Lenz testified that the omega-oxidation is "unrelated to what happens at the Q1 side chain." [*Id.* at 74:25-75:6; TEX 1341.0009 (Figure 10 illustrates that none of the metabolic pathways of the examined compound result in beta-oxidation of what corresponds to the Q^1 side chain).]

351. Dr. Lenz admitted that "this is a paper that one of skill in the art would have read in the relevant time period." [T. Tr., Feb. 24, 2009 P.M. 74:5-7.] Dr. Lenz, however, was not aware of the Newton paper at the time he formed his opinions in this case. [*Id.* at 74:8-10.]

352. "Pharmacologic and Pharmacokinetic Profile of SK&F S-106203, a Potent, Orally Active Peptidoleukotriene Receptor Antagonist, in Guinea Pig," written by D. W. P. Hay and others, including Dr. Gleason ("the Hay paper"), focuses on research done regarding a Smith Kline & French compound and would have been available to one of ordinary skill in the art at the time of the invention. [TEX 3360; T. Tr., Feb. 24, 2009 P.M. 76:1-7, 76:25-77:2 (Lenz).]

353. The Hay paper discusses the metabolic profile of another Smith Kline & French compound, SKF-106203, which is one of the ten compounds that a person of ordinary skill in the art would have known was in preclinical or clinical evaluation at the time of the invention. [T. Tr., Feb. 24, 2009 P.M. 76:25-77:2 (Lenz).] The Hay paper does not show evidence of beta-oxidation at what would be the Q^1 side chain of SKF-106203. [*Id.* at 77:3-10.]

354. The Hay paper, just like the Newton paper, does not show any evidence of beta-oxidation on the Q^1 side chain. [T. Tr., Feb. 24, 2009 P.M. 77:11-14 (Lenz).]

355. Dr. Gleason testified that a person of ordinary skill in the art would not have been motivated in 1990 to 1991 to make a substitution in the beta position of the Q^1 side chain because there was no suggestion that there was significant metabolism taking place. [T. Tr., Feb. 25, 2009 A.M. 96:6-8, 96:12-18, 96:21-97:10, 97:24-25.]

356. Dr. Lenz testified that a person of ordinary skill in the art would attach two methyl groups to the beta-carbon of the Q^1 side chain to avoid beta-oxidation. [T. Tr., Feb. 24, 2009 A.M. 130:25-131:6.] But without further explanation, other than that it's "[o]ne of the things that's listed in Merck's Patents (sic) 882 and EP093," Dr. Lenz suggests that a person of ordinary skill in the art would have replaced the two methyl groups (called a gem dimethyl substituent) with a cyclopropyl substituent. [*Id.* at 131:7-10.] While Dr. Lenz attempts to downplay the difficulty of synthesizing this particular substituent and its unlikely inclusion in such a compound by characterizing "[a] cyclopropyl ring [as] basically [] just connecting the two methyl groups together." [*Id.* at 10-12.]

357. Dr. Gleason disagreed that such a substitution would be so simple. Dr. Gleason testified that "in this timeframe, 1990, cyclopropyl groups were not easy to make" and that "[c]yclopropyl is not that commonly used." [T. Tr., Feb. 25, 2009 A.M. 100:10-19.] The two methyl groups of a gem dimethyl would stop the beta-oxidation just as effectively as a cyclopropyl group and is far easier. [*Id.*] Therefore, even if a person of ordinary skill in the art would have been concerned about beta-oxidation, they would not have been motivated to include a cyclopropyl substituent at the beta-position of the Q^1 side chain.

I. Secondary Considerations Confirm the Validity of Claims 18-22

358. Even if the Court determines that Teva has established a prima facie case of obviousness as to claims 18-22 of the '473 patent, the secondary considerations present in this case warrant a finding of nonobviousness.

359. All secondary considerations point towards the validity of the '473 patent, including the incredible commercial success of Singulair® tablets, the fact that Teva seeks to create a generic copy of Merck's Singulair® tablets, Singulair® tablets' satisfaction of the long-felt but unmet need of an alternative therapy for asthma and allergic rhinitis, the unexpected and surprising results of montelukast, the failure of so many others to create a safe and effective leukotriene antagonist, and the considerable praise awarded to the creators of montelukast.

1. Singular's Commercial Success Reflects the Benefits of the Invention

360. Merck asked Dr. Christopher A. Vellturo to opine on the relationship between the commercial success of Singulair® tablets and the properties of montelukast. [T. Tr., Feb. 25, 2009 P.M. 84:18-22 (Vellturo).] Dr. Vellturo found that the commercial success of Singulair® tablets is primarily attributable to the claimed features of the '473 patent. [*Id.* at 97:18-21, 102:16-103:22.]

361. Dr. Vellturo received an undergraduate degree from Brown University in Applied Mathematics and Economics and a Ph.D. from Massachusetts Institute of Technology in Industrial Organization and Econometrics. [T. Tr., Feb. 25,

2009 P.M. 82:23-83:5 (Vellturo).] Dr. Vellturo teaches economics at the Business School of Brown University and also works as an economist. [*Id.* at 83:13-16.] Dr. Vellturo has examined how commercial issues impact the pharmaceutical industry extensively. [*Id.* at 83:17-84:17.]

362. Sales of Singulair® pharmaceutical products from 1998, the year it was first introduced, through 2007 totaled some $14 billion dollars. [T. Tr., Feb. 25, 2009 P.M. 88:18-25 (Vellturo).]

363. Dr. Adam Jaffe, Teva's expert on commercial success, admitted that sales of $14 billion dollars constitute commercial success. [T. Tr., Feb. 23, 2009 P.M. 112:25-113:3.]

364. A drug is considered to be a blockbuster drug when its worldwide sales exceed $1.0 billion dollars in any given year. [T. Tr., Feb. 25, 2009 P.M. 89:4-10 (Vellturo).]

365. In 2007, Singulair® sales in the United States totaled $3.0 billion dollars; worldwide totals topped $4.3 billion dollars. [T. Tr., Feb. 25, 2009 P.M. 88:23-25 (Vellturo).]

366. Singulair® is a blockbuster drug. [T. Tr., Feb. 25, 2009 P.M. 88:19:25, 89:4-10 (Vellturo).]

367. Since Singulair® pharmaceutical products were introduced in the United States market, approximately 164 million prescriptions have been filled. In 2007 alone, 28 million prescriptions were filled. [T. Tr., Feb. 25, 2009 P.M. 89:13-17 (Vellturo).]

368. The market for allergic rhinitis medications is crowded with prescription medications, both generic and branded, as well as OTC (over-the-counter) medications. [T. Tr., Feb. 25, 2009 P.M. 90:12-17 (Vellturo).] Singulair® prescriptions account for 34 percent of asthma-related prescriptions, and 11 percent of all allergic rhinitis-related prescriptions. [*Id.*]

369. Singulair® prescriptions have steadily increased since 1998. [T. Tr., Feb. 25, 2009 P.M. 91:10-19 (Vellturo).]

370. Accolate® is the only other leukotriene antagonist that has been approved for sale by the FDA. [T. Tr., Feb. 25, 2009 P.M. 94:20-23 (Vellturo).]

371. Accolate® sales rose during 1996 and 1997, before Singulair® entered the market in 1998. [T. Tr., Feb. 25, 2009 P.M. 95:1-6 (Vellturo).] Singulair® tablets went on the market on or around February 20, 1998.

372. As sales of Singulair® pharmaceutical products increased, sales of Accolate® decreased to a fifth of what they had been at prior to the introduction of Singulair® tablets. [T. Tr., Feb. 25, 2009 P.M. 89:5-9 (Vellturo).]

373. Singulair® pharmaceutical products displaced Accolate® in the market for leukotriene antagonists, suggesting that Singulair® is preferred over Accolate®. [T. Tr., Feb. 25, 2009 P.M. 95:10-19 (Vellturo).]

374. The purpose of Merck's advertising for Singulair® pharmaceutical products is to educate customers about the features of the product. [Williams Dep. Tr. 109:13-14.]

375. In deciding whether a medication is an appropriate treatment for any given client, physicians consider the efficacy of the product, the safety profile of the product, the formulations that are available for the product, and the clinical data that is in support of the product. [Williams Dep. Tr. 41:1-16.]

376. Physician surveys conducted by a third party survey firm indicate that physicians prescribe Singulair® pharmaceutical products because the products are convenient, easy to use, and encourage patient compliance, furthering the real-world effectiveness of the medication. [T. Tr., Feb. 25, 2009 P.M. 98:1-99:2 (Vellturo).]

377. Though Dr. Jaffe suggested that advertising expenditures present a significant barrier to entry in the pharmaceutical market, he never measured the effect of any barrier to entry specifically in the asthmatic pharmaceutical market. [T. Tr., Feb. 23, 2009 P.M. 114:22-115:1 (Jaffe).]

378. Dr. Jaffe admitted that a large number of companies made significant research investments in trying to discover an LTD_4 antagonist. [T. Tr., Feb. 23, 2009 P.M. 115:2-5.]

379. It may take more than a billion dollars to bring a drug to market. [Snodgrass Dep. Tr. 199:7-25.]

380. Dr. Jaffe admitted that many companies tried to develop an antagonist for years, and clearly weren't deterred by any barrier to entry. [T. Tr., Feb. 23, 2009 P.M. 115:6-10, 15-16.]

381. Dr. Jaffe agreed that informational advertising is advertising which gives information about the substance of Singulair® and explains why it may be an appropriate treatment for a given patient. [T. Tr., Feb. 23, 2009 P.M. 116:6-11.]

382. Dr. Jaffe also agreed that promotional advertising is advertising that is not related to the substance or merits of the advertised product. [T. Tr., Feb. 23, 2009 P.M. 115:17-116:5.]

383. In developing his opinions, Dr. Jaffe did not examine Singulair® advertisements to determine whether they were informational or persuasive. [T. Tr., Feb. 23, 2009 P.M. 117:3-7 (Jaffe).]

384. The numerical analyses Dr. Jaffe prepared in an attempt to demonstrate a correlation between direct-to-consumer (DTC) advertising and the number of prescriptions filled did not distinguish between informational advertising and promotional advertising. [T. Tr., Feb. 23, 2009 P.M. 119:3-15 (Jaffe).]

385. The fact that doctors may have attended educational dinners that discussed Singulair® is not evidence that new prescriptions are resulting from anything other than the intrinsic and unique properties of Singulair®. [T. Tr., Feb. 23, 2009 P.M. 116:6-17 (Jaffe).] Dr. Eli O. Meltzer, Merck's medical expert, testified that educational dinners "are very informative" and explained that he has been a speaker at a number of such dinners over the years as a way of sharing his deep commitment to his practice and his patients. [T. Tr., Feb. 25, 2009 P.M. 69:8-20.]

386. The document that Dr. Jaffe relied on in making comments about these educational dinners explains that changes in a doctor's prescribing behavior that occur after these dinners are attributable to the merits of Singulair®. [T. Tr., Feb. 23, 2009 P.M. 115:17-20; 121:3-122:5 (Jaffe).]

387. Dr. Jaffe acknowledged that informational advertising would not be evidence against commercial success. [T. Tr., Feb. 23, 2009 P.M. 117:8-21.]

388. Dr. Jaffe agreed that Merck spends less on advertising Singulair® than some of Merck's competitors do in advertising competing products. [T. Tr., Feb. 23, 2009 P.M. 118:12-15.]

389. Dr. Jaffe admitted that some results of his statistical analyses could be used in a misleading way. [T. Tr., Feb. 23, 2009 P.M. 122:6-23.]

390. Dr. Jaffe acknowledged that his analysis demonstrated that sales of Singulair® pharmaceutical products are less sensitive to advertising than sales of other asthma and allergic rhinitis medications. [T. Tr., Feb. 23, 2009 P.M. 123:3-24.]

391. According to Dr. Jaffe's analysis, for every dollar of advertising spent on asthma and allergic rhinitis medications, pharmaceutical companies receive a return, on average, of $3.60. For every dollar of advertising Merck spends on Singulair® pharmaceutical products, the average return is only $1.67. [T. Tr., Feb. 23, 2009 P.M. 123:3-24 (Jaffe).]

392. From 2003 to 2007, the amount Merck spent on promotional spending for Singulair® pharmaceutical products decreased. [T. Tr., Feb. 23, 2009 P.M. 125:11-23 (Jaffe).]

393. Dr. Jaffe agreed that some portion of the $14 billion dollars resulting from the sale of Singulair® pharmaceutical products is attributable to the fact that Singulair® pharmaceutical products are a safe and effective means of treating a serious disease. [T. Tr., Feb. 23, 2009 P.M. 127:21-25.]

2. Teva Copied Singular Because it is Inventive

394. The labeling and/or package insert submitted with Teva's ANDA No. 78-605 states that the generic tablets are indicated for asthma, allergic rhinitis (seasonal and perennial), and exercise-induced bronchoconstriction. [Docket Entry No. 62, Revised Final Pretrial Order, Stipulated Fact 6.]

395. "The labeling proposed for the TEVA Pharmaceuticals USA drug product [10 mg montelukast sodium tablets] is the same as the labeling for the listed drug excerpt for [minor, non-substantive changes." [TEX 3003.0080; *see also* TEX 3008 (side-by-side comparison of labels).]

396. The labeling and/or package insert submitted with Teva's ANDA No. 78-723 states that the generic tablets are indicated for asthma, allergic rhinitis (seasonal and perennial), and exercise-induced bronchoconstriction. [Docket Entry No. 62, Revised Final Pretrial Order, Stipulated Fact 14.]

397. The proposed labeling and package insert proposed for the Teva drug product [4 and 5 mg montelukast sodium chewable tablet] is nearly identical to the labeling and package insert contained on Merck's 4 and 5 mg Singulair® product. [*See* TEX 3009.]

398. Teva's montelukast sodium chewable tablets are bioequivalent to Merck's Singulair® chewable tablets. [TEX 3004.0001, 0009.]

3. Singular Met a Long-Felt but Unsolved Need

399. None of the treatment options available in 1991 for either asthma or allergic rhinitis addressed the role that leukotrienes play in either asthma or allergic rhinitis. [T. Tr., Feb. 25, 2009 P.M. 54:13-18 (Meltzer).] Therefore, there "was an important mediator" for both diseases, LTD_4, "that really had nothing to antagonize it." [*Id.* at 54:24-25.]

400. As of 1991, there was a need for a treatment that would address the role of leukotrienes in asthma and allergic rhinitis. [T. Tr., Feb. 25, 2009 P.M. 55:4-9 (Meltzer).]

401. Merck's expert Dr. Meltzer opined on the state of the art regarding available treatments for asthma and allergic rhinitis before the 1991 timeframe and compared Singulair® tablets to those treatments. [T. Tr., Feb. 25, 2009 P.M. at 36:24-37:13 (Meltzer).] Dr. Meltzer received his undergraduate degree from the University of

Pennsylvania and went to medical school at Jefferson Medical College. [*Id.* at 35:8-10.] Dr. Meltzer completed his internship at Michael Reese in Chicago, Illinois, and his residency in pediatrics at St. Christopher's in Philadelphia, Pennsylvania, before undergoing allergy training at the National Jewish Hospital and Research Center in Denver, Colorado. [*Id.* at 35:11-15.] Dr. Meltzer is board certified in pediatrics and in allergy and immunology. [*Id.* at 35:17-18.] Dr. Meltzer has been specializing in the treatment of asthma, allergies, and related diseases for forty years, [*Id.* at 35:3-5], and has received several honors for his work in these fields. [*Id.* at 35:21-36:1.] Dr. Meltzer currently practices with the Allergy and Asthma Medical Group and Research Center in San Diego, California, and is also a Clinical Professor of Pediatrics at the University of California in San Diego. [*Id.* at 34:13-14, 34:24-25.] Dr. Meltzer has also been involved in clinical evaluations "for 50, 60 different companies," [*Id.* at 80:25-81:5], including one for Teva just days before his testimony in this case. [*Id.* at 36:18-23.]

402. Both Dr. Meltzer and Teva's medical expert, Dr. Peter J. Barnes, operate referral practices. [T. Tr., Feb. 25, 2009 P.M. 77:18-78:2 (Meltzer); T. Tr., Feb. 4, 2009 7:14-16 (Barnes).] As such, their population of patients differs from the general population of patients because their patients' primary care physicians have been unable to adequately care for the patients. [*Id.*]

403. The Global Initiative for Asthma ("GINA") is a worldwide effort to promulgate and maintain up-to-date treatment recommendations for the treatment of asthma. [T. Tr., Feb. 4, 2009 13:4-20 (Barnes).] A similar program has been adopted within the United States, the National Asthma Education and Prevention Program ("NAEPP"). [T. Tr., Feb. 25, 2009 P.M. at 40:5-9 (Meltzer).] Both programs focus on controlling the asthma of particular patients by focusing on continuing to monitor patients, reassess those patient's conditions, and based on that reassessment, maintaining or changing therapeutic interventions. [*Id.* at 41:16-42:8, 43:21-44:2.]

404. Educating patients about their condition and continuing to monitor patients is especially important because all patients do not react the same to treatments, and even patients that benefit from certain treatments do not necessarily do so to the same degree. [T. Tr., Feb. 25, 2009 P.M. 43:11-44:2 (Meltzer).]

405. Even with respect to a single patient, that patient may benefit from a variety of treatments depending on certain circumstances and changing needs over time. [T. Tr., Feb. 25, 2009 P.M. 44:3-16 (Meltzer).]

406. As of 1991, there were several different types of medications available for the treatment of asthma, the most important ones being: short-acting beta agonists, inhaled corticosteroids (and oral corticosteroids), and long-term beta agonists.

i. Short-Acting Beta Agonists

407. Short-acting beta agonists help reduce bronchospasm but do not address the underlying problem of inflammation. [T. Tr., Feb. 25, 2009 P.M. 45:8-9, 46:5-6 (Meltzer).]

408. Because short-acting beta agonists do not address the underlying inflammation, they are useful only as "rescue" medications that allow for the quick relief of acute asthma symptoms but that would not be suitable for long term use as treatment. [T. Tr., Feb. 25, 2009 P.M. 45:18-23, 46:5-6 (Meltzer).]

409. Short-acting beta agonists can cause people to become shaky if they are used too frequently. [T. Tr., Feb. 25, 2009 P.M. 46:11-12 (Meltzer).]

410. Generally, if a person is using a short-term beta agonist every night or multiple times throughout the day, this suggests that the person's asthma is probably not well controlled. [T. Tr., Feb. 25, 2009 P.M. 46:12-16 (Meltzer).]

ii. Inhaled Corticosteroids

411. Inhaled corticosteroids became available in the mid-1970s and are generally much safer than the oral corticosteroids used prior to their introduction. [T. Tr., Feb. 25, 2009 P.M. 46:23-3 (Meltzer).] Oral corticosteroids are absorbed systemically throughout the body and cause several severe side effects, such as oral thrush, glaucoma, cataract formation, bone demineralization, and stunted growth in children. [T. Tr., Feb. 25, 2009 P.M. at 47:6-12 (Meltzer); T. Tr., Feb. 4, 2009 25:20-23 (Barnes).]

412. Inhaled corticosteroids generally avoid these side effects at low doses, but approximately 50 percent of patients cannot gain control of their asthma with doses of corticosteroids at or below the dosage recommended by the GINA guidelines to avoid side effects. [T. Tr., Feb. 4, 2009 104:12-16 (noting that the GINA guidelines suggest that side effects are not an issue at doses of 400 milligrams of budesonide or below), 105:8-14 (noting that approximately 50 percent of patients cannot gain control of their asthma at doses of budesonide of 400 milligrams or below) (Barnes).]

413. Even in usual doses, inhaled corticosteroids are associated with some side effects; thrush can occur, and dystonia is not uncommon. [T. Tr., Feb. 25, 2009 P.M. 47:24-25 (Meltzer).] "If you inhale a lot of corticosteroids (sic), it can change the muscle system in the voice and it affects it. [A]nd [you] can get in children growth slowing and [you] can get skin thinning and bruising if you use high enough doses." [*Id.* at 48:6-10.]

414. Treatment with inhaled corticosteroids generally requires treatment on a twice daily basis. [T. Tr., Feb. 4, 2009 27:23-24 (Barnes).]

iii. Long Acting Beta Agonists

415. Long acting beta agonists are similar to short acting beta agonists, but they are not a fast-acting in relieving symptoms and they last longer. [T. Tr., Feb. 25, 2009 P.M. 48:14-17 (Meltzer).]

416. Long acting beta agonists carry what is known as a "black box" warning, which means that the drug packing must contain a block box warning that the product has been associated with increased chance of death. [T. Tr., Feb. 25, 2009 P.M. at 49:16-20 (Meltzer); T. Tr., Feb. 4, 2009 81:9-22 (Barnes).] Long acting beta agonists are also associated with less serious side effects that include tremors and some cardiovascular problems. [T. Tr., Feb. 25, 2009 P.M. 49:4-8 (Meltzer).]

417. Long acting beta agonists are never used on their own and are always used in conjunction with inhaled corticosteroids. [T. Tr., Feb. 25, 2009 P.M. 49:21-22 (Meltzer).]

iv. Drugs Targeting the LTD_4 Mediator

418. Teva's medical expert Dr. Barnes testified that "leukotriene D_4 has always been recognized as an important bronchoconstrictor mediator of asthma." [T. Tr., Feb. 4, 2009 83:12-14 (Barnes).] For this reason, compounds blocking the activity of LTD_4 were attractive targets in 1991. [T. Tr., Feb. 25, 2009 P.M. 54:13-18, 54:24-25 (Meltzer).]

419. Montelukast, the active ingredient in Merck's Singulair® tablets, is such a compound.

420. Merck sells Singulair® pharmaceutical products in the following forms: a 4 mg granules packet (for children 12 months–5 years of age), a 4 mg cherry chewable tablet (for children 2–5 years of age), a 5 mg cherry chewable tablet (for children 6–14 years of age), and a 10 mg tablet that is swallowed whole (for adults and adolescents 15 years and older). [Docket Entry No. 62, Revised Final Pretrial Order, Stipulated Fact 38.]

421. The FDA approved the use of Singulair® tablets (10 mg) for the prophylaxis and chronic treatment of asthma in patients 15 years of age and older on February 20, 1998. [Docket Entry No. 62, Revised Final Pretrial Order, Stipulated Fact 41.]

422. The FDA approved the use of Singulair® chewable tablets (5 mg) for the prophylaxis and chronic treatment of asthma in pediatric patients from 6 to 14 years of age on February 20, 1998. [Docket Entry No. 62, Revised Final Pretrial Order, Stipulated Fact 42.]

423. The FDA approved the use of Singulair® 4 mg chewable tablets for the prophylaxis of asthma in pediatric patients ages two to five on March 3, 2000. [Docket Entry No. 62, Revised Final Pretrial Order, Stipulated Fact 43.]

424. The FDA approved the use of Singulair® 4 mg chewable tablets for long term chronic treatment of asthma in children two to five years of age on November 23, 2001. [Docket Entry No. 62, Revised Final Pretrial Order, Stipulated Fact 44.]

425. The FDA approved the use of Singulair® tablets and chewable tablets for the relief of symptoms of seasonal allergic rhinitis for adults and pediatric patients two years of age and older on December 31, 2002. [Docket Entry No. 62, Revised Final Pretrial Order, Stipulated Fact 45.]

426. The FDA approved the use of Singulair® tablets, chewable tablets, and oral granules for the relief of symptoms of perennial allergic rhinitis ("PAR") in adults and pediatric patients six months of age and older on July 27, 2005. [Docket Entry No. 62, Revised Final Pretrial Order, Stipulated Fact 46.]

427. The FDA approved the use of Singulair® tablets, chewable tablets, and oral granules for the prevention of exercise-induced bronchoconstriction ("EIB") in patients 15 years of age and older on April 13, 2007. [Docket Entry No. 62, Revised Final Pretrial Order, Stipulated Fact 47.]

428. Dr. Meltzer has personal experience prescribing montelukast and uses montelukast in his clinical practice on a daily basis. [T. Tr., Feb. 25, 2009 P.M. 55:12-14, 56:4-5 (Meltzer).]

429. Dr. Meltzer prescribes montelukast for the treatment of both asthma and allergic rhinitis "because it's clearly effective" in treating both the upper airway and lower airway. [T. Tr., Feb. 25, 2009 P.M. 61:9-13 (Meltzer).]

430. Montelukast, the active ingredient in Singulair® tablets, can be taken once a day and remain effective. [T. Tr., Feb. 25, 2009 P.M. 60:6-20.] This is very important because "[i]t's much easier to get medicine into somebody once a day." [*Id.*] Montelukast is preferred because it is orally active, which means there is no need for inhalers. [T. Tr., Feb. 25, 2009 P.M. 58:23-59:17; *see also* T. Tr., Feb. 4, 2009 66:14-16 ("there is no doubt that patients initially prefer tablets because they are easy to take").] Dr. Meltzer testified that "the adherence rate is clearly better with an oral once a day medicine and that's as good a regime as any." [*Id.* at 61:6-8.]

431. Singulair® tablets are the only LTD_4 antagonist that is indicated for once-a-day use. [Philips Dep. Tr. 184:16-20.]

432. Montelukast is also very useful for the treatment of children because taking medication orally, especially in powdered or chewable form, is generally easier for children than taking medication with the use of an inhaler, as is required with the use of inhaled corticosteroids. [T. Tr., Feb. 25, 2009 P.M. 59:4-17 (Meltzer).]

433. Dr. Meltzer testified that montelukast is "extraordinarily safe. It is so safe that actually it has gotten a category B rating from the FDA which allows it to be

used in pregnancy [while] others have some consequences." [T. Tr., Feb. 25, 2009 P.M. 60:1-4.]

434. Studies of montelukast clearly document its effectiveness. [T. Tr., Feb. 25, 2009 P.M. 57:7-8 (Meltzer); *see, e.g.*, TEX 3128 (cross-referenced as TEX 3303) (showing that some patients respond better to montelukast than to inhaled corticosteroids).]

435. Dr. Meltzer testified that "[m]ontelukast has been shown to improve quality of life" in quantitative measures. [T. Tr., Feb. 25, 2009 P.M. 56:14-57:8.]

436. The only other commercially available leukotriene antagonist is zafirlukast, sold under the trade name Accolate®. [T. Tr., Feb. 25, 2009 P.M. 67:18-21.] Accolate® exhibits several undesirable properties: it must be taken twice a day instead of once a day; it must be taken one hour before or two hours after a meal; and most importantly, it was associated with hepatic toxicities. [*Id.* at 66:25-67:11.] Dr. Meltzer testified that these reasons led him and many others to switch over to montelukast as soon as it became available. [*Id.* at 67:11-13.]

437. Dr. Meltzer does not think he has prescribed Accolate® in the last ten years. [T. Tr., Feb. 25, 2009 P.M. 67:16-17 (Meltzer).]

438. There is also a leukotriene inhibitor, zilutin, that is commercially available, which also targets the LTD_4 mediator but does so by trying to inhibit the initial release of leukotriene. [T. Tr., Feb. 25, 2009 P.M. 67:21-68:2 (Meltzer).] Zilutin was approved by the FDA to be sold under the trade name Zyflo®, but this compound is associated with significant liver toxicity issues. [*Id.* at 68:1-10.] Patients on Zyflo® must submit to liver function studies on a regular basis, which discourages many people from taking the drug. [*Id.*] In addition, the drug had to be taken four times a day, and the pill was very large – both factors that would discourage patient acceptance. [*Id.* at 68:13-17.]

v. Treatment options for allergic rhinitis

439. Before 1991, the only treatment options in terms of available drugs for allergic rhinitis were the old generation anti-histamines, nasal decongestants, and internasal steroids. [T. Tr., Feb. 25, 2009 P.M. 52:13-53:1 (Meltzer).] Old generation anti-histamines caused drowsiness, and the then-available nasal decongestants either didn't work or caused problems. [*Id.*] Some internasal steroids worked. [*Id.*]

440. Decongestants in particular are generally not recommended as treatment for allergic rhinitis, because they can have rebound effects, meaning that when the patient stops taking the decongestant the rhinitis can get even worse than it was before. [T. Tr., Feb. 4, 2009 36:10-19 (Barnes).]

vi. Singulair filled a need as alternative treatment for both asthma and allergic rhinitis medications

441. None of the treatment options available in 1991 for either asthma or allergic rhinitis addressed the role that leukotrienes play in either asthma or allergic rhinitis. [T. Tr., Feb. 25, 2009 P.M. 54:13-18 (Meltzer).] Therefore, there "was an important mediator" for both diseases "that really had nothing to antagonize it." [*Id.* at 54:24-25.]

442. As of 1991, there was a need for a treatment that would address the role of leukotrienes in asthma and allergic rhinitis. [T. Tr., Feb. 25, 2009 P.M. 55:4-9 (Meltzer).]

443. It is desirable to be able to treat both asthma and allergic rhinitis with the same drug, as approximately 30-35 percent of people with allergic rhinitis have asthma and between 80 and 90 percent of those with asthma have allergic rhinitis. [T. Tr., Feb. 25, 2009 P.M. 61:24-62:3 (Meltzer).]

444. Dr. Meltzer testified that montelukast is "clearly effective" in treating both asthma and allergic rhinitis. [FF 429.]

445. No other single medication is approved for the treatment of both asthma and allergic rhinitis. [T. Tr., Feb. 25, 2009 P.M. 62:6-15 (Meltzer).]

446. Teva's expert, Dr. Barnes, agrees that "anti-leukotrienes such as SINGULAIR are effective treatments for asthma in that they can reduce symptoms and improve lung function. And they're safe and are given as a tablet once a day. So they are convenient." [T. Tr., Feb. 4, 2009 32:21-25, 33:2.] According to Dr. Barnes, "[t]here is no doubt that SINGULAIR has some efficacy in both asthma and rhinitis." [*Id.* at 70:9-11.] And "there is no doubt that it improves asthma control in children." [*Id.* at 93:16-17.] Dr. Barnes also agrees that montelukast is effective in the prevention of exercise-induced bronchoconstriction. [*Id.* at 93:18-21.]

447. The GINA guidelines recommend the use of montelukast as an accepted management therapy for the treatment of asthma. [T. Tr., Feb. 4, 2009 79:17-25, 80:2-3 (Barnes).] And because montelukast is exceptionally safe, the GINA guidelines provide that the use of montelukast would be "appropriate particularly for patients who are unable or unwilling to use inhaled corticosteroids or who experience intolerable side effects, such as persistent hoarseness from inhaled glucocorticosteroid treatment and those with concomitant allergic rhinitis." [TEX 3304.0079.]

448. Not everyone responds to a particular treatment in the same way, so it is important to tailor the treatment to the individual. [FF 404.] "Oral Montelukast, Inhaled Beclomethasone, and Placebo for Chronic Acid," written by Kerstin Malmstrom and others ("the Malmstrom paper"), compares the clinical benefits of montelukast to that of beclomethasone, an inhaled corticosteroid. [TEX 3128 (cross-referenced as TEX

3303).] The Malmstrom paper demonstrates that although Dr. Barnes may be correct that inhaled corticosteroids are more effective than montelukast for the majority of patients, that is not true for all patients. [*Id.* at 0006; T. Tr., Feb. 25, 2009 P.M. 64:11-65:16 (Meltzer).] In fact, some patients do not benefit from inhaled corticosteroids at all, and those same patients may respond to montelukast. [*See id.*]

449. Dr. Meltzer emphasized the need to focus on individuals, not averages, when evaluating medical treatment:

> Q. When you treat patients, are you treating an average?
>
> A. I never treat average. I treat an individual and each person is precious, whether it's a child or it's an adult. They need to have themselves listened to, responded to, cared for in an ongoing, meaningful way.
>
> [T. Tr., Feb. 25, 2009 P.M. 81:7-12.]

450. Montelukast is sometimes used as an add-on therapy to inhaled corticosteroids for patients whose asthma cannot be controlled with inhaled corticosteroids alone. [T. Tr., Feb. 25, 2009 P.M. 65:24-66:10 (Meltzer).]

451. "Effect of Montelukast on Exhaled Leukotrienes and Quality of Life in Asthmatic Patients," written by Wojciech A. Biernacki and others, including Teva's medical expert Dr. Barnes, concludes that the addition of montelukast to the therapy of patients whose asthma was otherwise uncontrolled with the use of corticosteroids alone resulted in a significant improvement in patients' quality of life. [TEX 3292.0002; T. Tr., Feb. 4, 2009 87:3-6, 87:10-21 (Barnes).]

452. Long-term beta agonists can also be used as add-on therapy to inhaled corticosteroids, but long-term beta agonists must be sold with a black box warning because their use has been linked to an increased risk of death. [FF 416.] Montelukast not only presents an alternative to those people wary of or unwilling to take a medication subject to a black box warning, it is so safe that even pregnant women can take montelukast. [FF 433.]

453. Dr. Meltzer believes that montelukast has fulfilled the unmet need of providing a safe and effective treatment that addresses the role of leukotrienes in both asthma and allergic rhinitis:

> Q. In your experience, are there many patients who benefit from montelukast who did not benefit from corticosteroids (sic)?

> A. There are patients who benefit from leukotriene modifiers such as montelukast who do not benefit from inhaled corticosteroids (sic), yes.
>
> Q. Are there also patients who benefit from the addition of montelukast to a corticosteroid (sic) regime (sic)?
>
> A. Yes.
>
> [T. Tr., Feb. 25, 2009 P.M. 81:12-21.]

4. Montelukast Exhibits Many Unexpected Results

454. When Mr. Belley suggested attaching a tertiary alcohol to the right-most phenyl ring, both Robert Zamboni and Dr. Young, the creator of the model, said that the tertiary would not work. [Belley Dep. Tr. 36:19-37:4; Leger Dep. Tr. 88:7-16 (The tertiary alcohol suggestion "was discussed with Robert Zamboni, and I think also Marc Labelle could have been there. [Belley] suggested that, and the initial response was not necessarily to go in that direction."); *id.* at 89:22-25 ("I can't speak for Zamboni, but at the time they were more laughing about the suggestion."); Zamboni Dep. Tr. 35:1-21 (When Mr. Belley approached Zamboni about the tertiary alcohol, Zamboni "looked at him and sa[id], 'Don't even bother testing it. It's going to be unstable [because] tertiary alcohols are well-known to be unstable chemically.'").]

455. Dr. Zamboni continued to tell Mr. Belley that Mr. Belley was wasting his time on the tertiary alcohol, even when Mr. Belley was purifying the compound he had synthesized. [Belley Dep. Tr. 37:18-38:7.]

456. After Mr. Belley synthesized a compound containing a tertiary alcohol, "everybody was surprised to see its activity. They were surprised because it was active. They were surprised because it was more active than everything else at the time, and later there were surprised because it had good pharmacokinetics." [Belley Dep. Tr. 37:7-15, 54:18-24; *see also* Guay Dep. Tr. 47:2-4 ("[S]omeone had made a tertiary alcohol compound, and it had a very surprising and beneficial effect on the [pharmacokinetic] profile."); Zamboni Dep. Tr. 35:17-21.]

457. The Merck chemists were also surprised that the tertiary alcohol-containing compound demonstrated strong potency in part because a tertiary alcohol is not as polar as an amide. [Belley Dep. Tr. 116:15-18; Goshko Dep. Tr. 49:16-22; Xiang Dep. Tr. 66:13-67:15; T. Tr., February 23, 2009 A.M. 78:19-25 (Young).]

458. On the continuum of polarity, Dr. Young would place a tertiary alcohol on the less polar side. [T. Tr., February 23, 2009 A.M. 100:2-6 (Young).]

459. Dr. Guay testified in his deposition that a tertiary alcohol is only very slightly polar. [Guay Dep. Tr. 95:2-5.]

460. Dr. Zamboni explained that a tertiary alcohol is between a polar and non-polar group. "[Y]ou can't really call it either one." [Zamboni Dep. Tr. 37:22-24.]

461. Dr. Young's receptor model reflected his belief that a hydrophilic moiety was needed to have an effective LTD_4 antagonist. [TEX 3283.002.] Hydrophilic means "water-liking." As Dr. Young testified, "these alkyl groups on the tertiary alcohol are generally water-hating." [T. Tr., February 23, 2009 A.M. 80:11-17.]

462. Dr. Young believed that the B site of the LTD_4 receptor was hydrophilic, not lipophilic. [T. Tr., February 23, 2009 A.M. 85:3-10 (Young).]

463. Dr. Guay testified in his deposition that a tertiary alcohol is not hydrophilic. [Guay Dep. Tr. 90:15-24.]

464. Dr. Young explained that "a tertiary alcohol is a relatively large and bulky group. And it's also very lipophilic. . .. So it is really not what I thought would be efficient. . .. out of the many things we could make, that was not a great choice to start with." [T. Tr., February 23, 2009 A.M. 80:11-21.]

465. Even Mr. Belley was surprised: he testified in his deposition that the tertiary alcohol-containing compound worked a lot better than he had expected. [Belley Dep. Tr. 49:4-12.]

466. Mr. Belley also testified that the alcohol compound could have been completely inactive; the chemists would not have known without trying. [Belley Dep. Tr. 50:24-51:2; *see also* Guay Dep. Tr. 48:13-49:3.]

467. Dr. Gleason was surprised the first time he saw the structure of montelukast because the phenyl ring in the Q^2 side chain "was not something that [persons working in the field] had seen elsewhere." [T. Tr., Feb. 25, 2009 A.M. 48:13-15, 43:24-49:6 (Gleason).] There was nothing in the then-existing art suggesting that such a functional group would be desirable or effective in a leukotriene antagonist.

468. Dr. Gleason was also "very" surprised to see a tertiary benzylic alcohol (a tertiary alcohol connected directly to a phenyl ring, as in the Q^2 side chain of montelukast). [T. Tr., Feb. 25, 2009 A.M. 48:13-15, 49:7-10 (Gleason).] Dr. Gleason was "very surprised that [there] would be that kind of functionality in a drug" because he would have expected such a functional group to be very reactive in the acidic environment of the stomach. [*Id.* at 49:10-14.]

469. It is well known in organic chemistry that a tertiary alcohol is much more reactive than a primary alcohol and that an alcohol is much more reactive that an ordinary alcohol. [FF 268.]

5. Many Failed in their Efforts to Develop LTD_4 Antagonists

470. Dr. Gleason explained that a medicinal chemistry can find a starting point for developing a new drug in several ways: by screening large collections of compounds to find one with the desired properties, by starting with knowledge of the target structure and designing or engineering molecules that might bind to that target, by looking to the existing art in the field at the time, or by looking to the natural compound that binds to the receptor being targeted and trying to modify that compound to eliminate that part of the compound activating the receptor. [T. Tr., Feb. 25, 2009 A.M. 50:18-51:9.] Because nothing beyond the structure of LTD_4 was known in the field at the time Smith Kline & French began their leukotriene antagonist program, the team at Smith Kline & French adopted the last approach. [*Id.*]

471. Importantly, once a lead compound is selected and is modified, "each time you make a change you test the compound, . . . usually in your preliminary assays, the binding assay, your functional assay, to see if you have improved your activity." [T. Tr., Feb. 25, 2009 A.M. 52:4-8 (Gleason).] "[A]s you make a change, you try to learn from it and go back and think and improve your molecule. It's a very iterative process." [*Id.* at 52:20-22.] Throughout this process, it is important to test the new compounds after each modification; if you test a compound after making two or three changes and see an effect, you have no idea which of the changes caused that effect. [*Id.* at 53:5-10.]

472. This is a "very, very difficult process" that is "very, very resource intensive" and generally requires the synthesis of thousands of compounds. [T. Tr., Feb. 25, 2009 A.M. 54:3-4, 54:9-13, 60:8-13 (Gleason).]

473. Through this process, Smith Kline & French was able to produce two promising compounds: SK&F 104353 and SK&F 106203. [T. Tr., Feb. 25, 2009 A.M. 58:24-59:12, 59:19-60:7 (Gleason).] Both compounds were progressed into clinical development, but SK&F 104353 was ultimately abandoned because even though it worked, the compound didn't have the level of potency desired by Smith Kline & French was looking. [*Id.* at 59:9-12.]

474. SK&F 106203 exhibited particularly desirable features, including being very potent, having excellent oral bioavailability, and demonstrating about a 12 hour half-life in animal testing that suggested it could be used as a once-a-day drug. [T. Tr., Feb. 25, 2009 A.M. 59:1-12, 59:19-60:7 (Gleason).] But Smith Kline & French ultimately abandoned SK&F 106203 in favor of licensing another leukotriene antagonist from Ono, RS-411, because that drug was further progressed in clinical trials. [*Id.* at 60:22-61:9.]

475. Smith Kline & French eventually abandoned the Ono compound as well because the Ono compound did not meet expectations in late stage clinical trials. [T. Tr., Feb. 25, 2009 A.M. 61:7-11 (Gleason).]

476. Although the Ono compound has been marketed in Japan and a couple of other countries, it never received FDA approval to be used in the U.S. [T. Tr., Feb. 25, 2009 A.M. 61:12-15 (Gleason).]

477. In 1990 to 1991, all three of these compounds were known to be in clinical trials. [TEX 3131.0016 (SK&F 104353 in phase III clinical trials); TEX 3203.0002 (SK&F 106203 in trial and ONO-RS-411 in antigen challenge in man).] At that time, a person of ordinary skill in the art would have known of several other compounds in advanced stages of development as well, including compounds from Lilly, Revlon, Rhone-Poulenc Rorer, Wyeth, Leo, Merck and ICI. [T. Tr., Feb. 25, 2009 A.M. 61:22-63:5 (Gleason).]

478. Of all of these compounds, only the ICI compound, ICI-204,219, eventually made it to commercial development. [T. Tr., Feb. 25, 2009 A.M. 63:22-24, 64:3-4 (Gleason).] ICI-204,219 has been made commercially available as Accolate [*id.*] but as discussed in greater detail in the long-felt but unmet need section, even Accolate possessed several undesirable properties.

III. The ’473 Patent Was Not Procured through Inequitable Conduct

479. Teva’s inequitable conduct argument relies upon the nondisclosure of the Young ’89 model, as described in Young ’89. [*See* Docket Entry No. 73 at 9 (Defendants’ Pretrial Brief).]

480. Teva argues that Young ’89 would render claim 7 prima facie obvious, [T. Tr., Feb. 24, 2009 A.M. 124:18-20 (Lenz)], and that the combination of Young ’89 and the ’882 patent render claims 1 and 7 prima facie obvious. [*Id.*. 125:10-17.]

481. Teva has not shown by clear and convincing evidence that the Young ’89 model would have been material to the patentability of the ’473 patent, nor has Teva shown by clear and convincing evidence that Young ’89 was withheld by Merck during the prosecution of the ’473 patent with the intent to deceive the PTO.

482. Teva has not shown by clear and convincing evidence that Merck made any false or misleading statements to the PTO during the prosecution of the ’473 patent.

A. The Prosecution of the ’473 Patent

483. The ’473 patent was issued on October 15, 1996, from U.S. Patent Application Serial No. 08/392,592 (“the ’592 application”), which was filed on February

23, 1995. The '592 application is a continuation of U.S. Patent Application Serial No. 07/774,414, filed October 10, 1991 ("the '414 application"), which is a continuation-in-part of U.S. Patent Application Serial No. 07/741,888, filed August 8, 1991 ("the '888 application"), which is a continuation-in-part of U.S. Patent Application Serial No. 07/596,887, filed on October 12, 1990 ("the '887 application"). [Docket Entry No. 62, Revised Final Pretrial Order, Stipulated Fact 26.]

484. Mr. Gabriel Lopez was employed by Merck as a patent attorney from approximately 1977 to 1993. [T. Tr., Feb. 24, 2009 A.M. 6:12-25 (Lopez).] Mr. Lopez received a B.S. in chemistry from Fordham University in 1964 and a J.D. from St. John's School of Law. [*Id.* at 5:3-15.] Mr. Lopez is licensed to practice law in New Jersey and New York and is registered as a patent attorney with the United States Patent and Trademark Office. [*Id.* at 5:18-24.]

485. The '888 application was filed on August 8, 1991. The sole named inventor was Michel Belley. [Docket Entry No. 62, Revised Final Pretrial Order, Stipulated Fact 77.]

486. The '888 application added Examples 138, 139, 146, and 161. [Docket Entry No. 62, Revised Final Pretrial Order, Stipulated Fact 78.]

487. Montelukast is disclosed as Example 161. [Docket Entry No. 62, Revised Final Pretrial Order, Stipulated Fact 79.]

488. Claims 18-22 are entitled to a priority date pursuant to 35 U.S.C. § 120 no earlier than August 8, 1991, the filing date of the '888 application. [Docket Entry No. 62, Revised Final Pretrial Order, Stipulated Fact 107.]

489. While employed as a patent attorney at Merck, Mr. Lopez wrote and prosecuted several patent applications, including the patents to which the '473 patent claims priority. But Mr. Lopez did not file or prosecute the '473 patent. [T. Tr., Feb. 24, 2009 A.M. 7:1-7, 46:1-18 (Lopez).]

B. Young '89 Is Not Material

490. Young '89 is not material to the patentability of the '473 patent, and a reasonable examiner would not have wanted to know about the Young '89 model, as described in Young '89, when accessing the patentability of the '473 patent.

491. Dr. Gleason has reviewed all of the relevant materials – including the '473 patent and its file history – and testified that Young '89 does not render claim 7 prima facie obvious and that the combination of Young '89 and the '882 patent does not render claims 1 or 7 prima facie obvious. [T. Tr., Feb. 25, 2009 A.M. 101:10-102:13 (Dr. Gleason reviewed the '473 patent, the file history of the '473 patent, Dr. Lenz's expert opinions, the '409 patent, the '882 patent, EP '093, and EP '818), 107:5-9, 107:16-21.] Young '89 does not address things like steric requirements, the shape of the receptor, the

requisite polarity to bind with the receptor, and the directionality of potential hydrogen bonds. [*Id.* at 107:11-15, 107:23-108:4.] "Young 89 is very broad and very noninformative." [*Id.* at 107:14-15.]

492. Dr. Jorgensen reviewed Young '89 to determine whether it would be useful in drug design and determined that it would not. [T. Tr., Feb. 26, 2009 26:4-5 ("there's really no practical value to this that I can see").] Dr. Jorgensen testified that this is because in the Young '89 model "there is no detail as far as [he is] concerned that could allow one to progress in a sensible fashion towards a drug." [*Id.* at 26:8-11.]

493. Dr. Gleason reviewed both Young '88 and Young '89 to determine whether they would have been relevant to the patentability of the compounds in the '473 patent and determined that neither is relevant. [T. Tr., Feb. 25, 2009 A.M. 47:16-24 (Gleason).]

494. Dr. Young testified that the Young '89 model "was a state of what [he] knew about and [his] colleagues knew about the data that was available. But then that data was largely available to many other people." [February 23, 2009, a.m., T. Tr. 106:18-24.]

495. Dr. Lenz recognizes that people at these types of conferences "tend to be circumspect on what they tell the (sic) people in other companies" because "they don't want to share proprietary information with people who are in competition with them." [T. Tr., Feb. 24, 2009 A.M. 141:10-142:2.]

496. Dr. Gleason, Merck's medicinal chemistry expert, attended the presentation at the Taipei conference at which Dr. Young presented the Young '89 model. [T. Tr., Feb. 23, 2009 A.M. 72:22-24 (Young); Feb. 25, 2009 A.M. 64:14-17, 64:25-65:2 (Gleason).]

497. Dr. Young does not remember seeing Teva's medicinal chemistry expert, Dr. Lenz, at the Taipei conference. [T. Tr., February 23, 2009 A.M. 73:4-5 (Young).]

498. Dr. Gleason's reaction regarding the model at that time was that "it was nothing new. It was essentially the same conceptual model that [the Smith Kline & French scientists] has been working with ***almost from the beginning of our program***. It was essentially just a representation of the data from the early Corey work on analogs of LTD4 itself." [T. Tr., Feb. 25, 2009 A.M. 65:5-12 (emphasis added) (Gleason).]

499. Dr. Young explained that the model was not used as a blueprint for creating the "right" LTD_4 antagonist. Rather, it was only a general model that allowed the chemists to work in certain directions as opposed to other directions. [T. Tr., February 23, 2009 A.M. 79:2-9 (Young).]

500. At his deposition, Dr. Zamboni testified that the model makes suggestions, but does not teach or prove anything. "You have to remember that this model is a visualization. It's a carve – it's like a Picasso, right? Picasso's looks like a face, but you don't know what the face looks like. And that's really important in trying to describe this model." [Zamboni Dep. Tr. 20:24-21:5.]

501. Dr. Gleason acknowledged a similar level of utility for the model independently derived at Smith Kline & French: "[V]ery early on in the program it had some benefit to set some broad guidelines on where we were going, but very quickly it became, really, a non-entity. And that's because it really didn't – it didn't have the detail that would be necessary to actually direct a discovery effort." [T. Tr., Feb. 25, 2009 A.M. 65:15-19.]

502. Dr. Young testified that "many millions" of compounds could fit within the bounds of the conceptual receptor model. [T. Tr., February 23, 2009 A.M. 76:2-7.] Dr. Gleason similarly testified that "hundreds of thousands, millions" of compounds fit the Young '89 model. [T. Tr., Feb. 25, 2009 A.M. 66:1-4.] And Dr. Jorgensen opined that there is potentially "an infinity of molecules that can fit" the Young '89 model. [T. Tr., Feb. 26, 2009 26:20-21.]

503. Dr. Gleason testified that the Young '89 model would not provide any guidance as to distinguishing between any of the huge number of potential compounds that fit the model. [T. Tr., Feb. 25, 2009 A.M. 66:5-8.] Dr. Jorgensen agreed that the model "really doesn't help guide me in any way to decide which among that infinity of molecules that I would pursue." [T. Tr., Feb. 26, 2009 26:21-23.]

504. Despite being present at Dr. Young's presentation of the Young '89 model at the Taipei conference, the structure of montelukast did not become apparent to Dr. Gleason after observing the presentation. [T. Tr., Feb. 25, 2009 A.M. 30:8-10, 30:23-25 (Gleason).] Dr. Gleason explained that this is because the structure of montelukast "has so many structural changes from the compound that was being described [L-660,]711, that there's no way that you [] could look at it and get from [L-660,]711 to [m]ontelukast with just that model." [*Id.* at 31:1, 31:10-13.]

505. In fact, Merck developed many compounds that fit loosely within the Young '89 model but failed as effective and safe LTD_4 antagonists. [T. Tr., February 23, 2009 A.M. 79:10-14 (Young).]

506. Merck continued to develop and test hundreds and hundreds of additional compounds after the model was developed and presented. [T. Tr., February 23, 2009 A.M. 82:24-83:3 (Young).]

507. Though Mr. Belley developed the idea of using a tertiary alcohol after Dr. Young presented a conceptualized receptor model at an internal meeting, Mr. Belley never indicated that the model prompted this idea or otherwise motivated him to pursue the use of a tertiary alcohol. In fact, Mr. Belley made clear that the internal

meeting focused not on the model, but rather on a review of the company's overall LTD_4 antagonist work. [Belley Dep. Tr. 33:3-34:4.]

508. The Young '89 model did not come up during the conversation in which Mr. Belley suggested the use of a tertiary alcohol. [Leger Dep. Tr. 140:7-12.]

509. Nothing in Young '89 suggests the use of a tertiary alcohol in the Q2 position. [Belley Dep. Tr. 154:18-155:7.] Indeed, as inventor Michel Belley testified, the model disclosed in the Young publications "doesn't suggest anything . . . there is nowhere in the paper where they suggest testing alcohol. There is nowhere in the paper that suggests that an alcohol might be good there." [*Id.*]

510. When asked whether montelukast fits the Young '89 model, Mr. Belley responded: "When the model was developed by Bob Young and Bob Zamboni, when I suggested to put a tertiary alcohol there, they said it's not going to work. . . . [A]ccording to the reaction, the answer would be no. But I probably would have argued the other way around. So the answer is not a definitive yes or a definitive no. You are in a gray zone there. . . because the alcohol is not the same polarity as an acid or an amide, and it's also not the same kind of hydrogen bond or donor receptor. It's weaker. So chances are it could be active or could be not active. You don't know." [Belley Dep. Tr. 68:23-69:15.]

511. Dr. Leger testified that Dr. Young's internal presentation that included the Young '89 model "didn't bring new information to anyone." [Leger Dep. Tr. 132:4-23.]

512. Though Dr. Xiang was surprised that Young '89 had not been disclosed to the PTO during the prosecution of the '473 patent, Xiang's understanding of the duty of disclosure was incorrect. [Xiang Dep. Tr. 68:25-69:21.] Dr. Xiang believed that "all information prior to filing patent application which related to the subject should be submitted to the Patent Office." [*Id.*] The enacted standard only requires that an applicant disclose prior art that is material to the patentability of the claims.

513. The Merck chemists looked to LTD_4 itself, and not to a hypothetical receptor model, in attempting to develop a safe and effective LTD_4 antagonist. [Belley Dep. Tr. 24:11-17 ("The information we took out of LTD4 to help us design [an] antagonist was based on the structure of LTD4 itself, not on its way that [it] would hypothetically bind to the receptor.").]

514. "The model did not lead to the initial finding of what we call the lead compound, which is the styrylquinoline. That came out of pure screening on the guinea pig." [Zamboni Dep. Tr. 26:10-13.]

515. Dr. Labelle never used the Young '89 model in designing backup compounds to MK-571. When asked why, Dr. Labelle responded: "It doesn't really have any kind of value, as far as I am concerned. We're actually concerned with making

a backup to MK-571, so we start with MK-571 and change the structure. Having a representation that is vague about what is needed not something we use." [T. Tr., February 23, 2009 P.M. 6:12-21.]

516. Dr. Zamboni explained that he had no reaction to Young '89 model when Young showed it to him, and they did not discuss the model. [Zamboni Dep. Tr. 16:18-17:1.]

517. Young himself did not believe that the model suggested the use of an alcohol: When Dr. Young conceptualized the hypothetical LTD_4 model, he thought that the moiety binding at the "B" site should be both hydrophilic and "polar like an acid or an amide." [T. Tr., February 23, 2009 A.M. 78:19-25 (Young); TEX 3283.0002.]

518. On the continuum of polarity, Dr. Young would place a tertiary alcohol in the less polar end. [T. Tr., February 23, 2009 A.M. 100:2-6 (Young).]

519. Dr. Young's receptor model reflected his belief that a hydrophilic moiety was needed to have an effective LTD_4 antagonist. [TEX 3283.002.] Hydrophilic means "water-liking." As Dr. Young testified, "these alkyl groups on the tertiary alcohol are generally water-hating." [T. Tr., February 23, 2009 A.M. 80:11-17.]

520. Dr. Gleason testified that Young '89 and the Young '89 model described therein were included in the Kingsbury publication for the sole purpose of illustrating a concept: that medicinal chemists should approach problems rationally rather than simply modifying compounds with no direction whatsoever. [T. Tr., Feb. 25, 2009 A.M. 82:19-84:1.] To that end, the authors "literally took exactly what Young said in his paper and put it in [the Kingsbury publication.] The intent [] was not [to] say that the Merck work was the way to go. What [the authors] were trying to say is that the philosophy of trying to understand how the receptor binds to the receptor, that going down that rational design approach we thought was the way to go in the future." [*Id.* at 84:1-7.] This inclusion also must be viewed in light of the fact that rational drug design was just beginning to emerge, and examples of such design at any level were scarce. [*See id.* at 84:8-12.]

521. Despite Dr. Lenz having used models extensively in his 40 years of work as a medicinal chemist, his efforts never resulted in any drug that has actually been marketed. [T. Tr., Feb. 24, 2009 A.M. 139:14-25 (Lenz).]

522. Despite using essentially the same model as the Young '89 model since "very early on in the [Smith Kline & French] program," the Smith Kline & French scientists working on the development of leukotriene antagonists failed to develop a safe and effective leukotriene antagonist. [FF 498.]

C. Gabriel Lopez Did Not Make Any False or Misleading Statements

523. On May 22, 1992, the patent examiner issued a rejection of an application to which the '473 patent claims priority (U.S. Patent Application No. 07/774,414 ("the '414 application"). [TEX 1444.0602-606.]

524. Claims 1 through 17 of the '414 application were "rejected . . . under 35 U.S.C. § 103 as obvious over Young '409" because Young '409 disclosed examples where "Q_2 is CH_2-OH and Y = -CH=CH." [TEX 1444.0605-606.] As such, the examiner recognized that Young '409 disclosed compounds where the Q^2 could be a primary alcohol.

525. Mr. Lopez traversed the rejection on this ground in a response dated August 26, 1992. [TEX 1444.0607-609.]

526. Mr. Lopez's response stated that "[t]he present compounds differ from the art in that Q^2 is a secondary or tertiary alcohol or amine and that the present Z^1/Z^2=CONR^3. Any one of these differences would render the present compounds unobvious; the combination of three substantial differences appears irrefutable." [TEX 1444.0609.]

527. When Teva's own expert, Dr. Lenz, was asked whether he believed primary alcohols are different from secondary or tertiary alcohols, Dr. Lenz answered in the affirmative and identified several such differences:

> "There's two parts to that question. One part is, is that – they separate into two parts, one of which is the physical chemical properties and the other one is their chemical properties oxidated metabolic properties. In the first one where you have physical chemical properties like the ability to be non ionized, to be polar, to be able to hydrogen bond, there is no real difference between the primary and secondary and tertiary alcohols. . . .
>
> ***If you want to look at the metabolic, in the chemical portions of it, yes, there is a difference***. A primary alcohol is easily oxidized. It'll go to the aldehyde, it'll go to the acid. A secondary one will go to the ketone. In terms of metabolism that's important. In terms of receptor bonding, you're not going to get metabolism in a receptor. So yes, there are two different types."
>
> [T. Tr., Feb. 24, 2009 A.M. 114:12-115:6 (emphasis added).]

528. Dr. Lenz further testified that he believed Mr. Lopez's response to the PTO "is talking primarily about the chemical and metabolic aspects of it, the negative

parts of it as opposed to the positive parts which would be the physical chemical properties." [T. Tr., Feb. 24, 2009 A.M. 115:16-21.]

529. Regardless of which differences Mr. Lopez was referring to in his response, Dr. Lenz does acknowledge that some differences exist. And metabolic differences in a compound are relevant in determining the safety and the efficacy of a compound; in fact, Dr. Lenz's own purported obviousness analysis of montelukast relies heavily on such considerations. [*See, e.g.*, T. Tr., Feb. 24, 2009 A.M. 130:1-8, 132:5-14 (Lenz).]

530. Dr. Jorgensen, Merck's expert opining on the utility of the Young '89 model, testified that "[t]here isn't any interchangeability . . . between primary, secondary, and tertiary alcohols. They're very different beasts." [T. Tr., Feb. 26, 2009 30:2-4.] Primary alcohols are generally metabolized into an acid, secondary alcohols are generally metabolized into ketones, and tertiary alcohols are not generally used because they are reactive and decompose. [*Id.* at 30:5-9.]

531. Young '89 does not mention alcohols [FF 254], much less that a primary alcohol would be interchangeable with a secondary or tertiary alcohol. In fact, each of these groups have specific properties and characteristics that suggest they would not be interchangeable in a chemical compound.

532. Dr. Young testified that a tertiary alcohol is not interchangeable with a primary alcohol. [T. Tr., February 23, 2009 A.M. 83:8-14.]

533. Dr. Jorgensen testified that "[t]here isn't any interchangeability . . . between primary, secondary, and tertiary alcohols. They're very different beasts." [T. Tr., Feb. 26, 2009 30:2-4.]

534. Dr. Gleason testified that it is well known in organic chemistry that a tertiary alcohol is much more reactive than a primary alcohol and that a benzylic alcohol is much more reactive that an ordinary alcohol. [T. Tr., Feb. 25, 2009 A.M. 49:25-50:50.] Dr. Jorgensen agreed with this analysis: "Tertiary alcohols, particularly benzylic or allylic, are unstable and are expected to decompose in even mildly acidic (sic) conditions. So it is very unusual to see a tertiary alcohol on a drug." [T. Tr., Feb. 26, 2009 29:20-23.]

535. Dr. Zamboni also testified that tertiary alcohols are less stable than primary alcohols in the presence of acids. [Zamboni Dep. Tr. 45:14-15.]

536. The size of a potential antagonist is an important consideration in drug development. If chemists make a compound too large, it will not fit in the receptor site. [T. Tr., February 23, 2009 A.M. 84:16-23 (Young).]

537. Dr. Young testified that during the 1988-1989 time frame the available evidence suggested that a larger, bulkier group would be more problematic. [T. Tr. February 23, 2009, A.M. 86:1-4.]

538. Both tertiary alcohols and secondary alcohols are much larger than primary alcohols and therefore are not interchangeable. [T. Tr., Feb. 25, 2009 A.M. 77:19-22, 78:7-14 (Gleason).] A tertiary alcohol is at least three times the size of a primary alcohol, and a secondary alcohol is at least twice the size of a primary alcohol. [*Id.*]

539. Tertiary alcohols also differ from primary alcohols in that tertiary alcohols are less polar that primary alcohols. [T. Tr., Feb. 25, 2009 A.M. 76:7-8, 78:3-6 (Gleason).] Dr. Gleason testified that he would also expect that tertiary alcohols would differ from primary alcohols in their ability to hydrogen bond, especially because of interactions with the extra methyl groups on a tertiary alcohol. [*Id.* at 76:5-77:9.]

540. Mr. Lopez's response to the patent examiner does not specify on what grounds he is differentiating the secondary and tertiary alcohols in the '414 application, just that "[t]he present compounds differ from the art" in question based on the presence of secondary and tertiary alcohols. [*see* TEX 1444.0609.] Therefore, the admissions by Teva's own expert dictate that Teva cannot contend that these statements to the examiner are false or misleading.

541. In fact, Dr. Lenz admitted that Mr. Lopez's statement was true. [T. Tr., Feb. 25, 2009 A.M. 6:10-24 (Lenz).]

542. Mr. Lopez's statements were nothing more than attorney argument to the patent examiner and should not be subject to the severe penalty of inequitable conduct.

D. Inequitable Conduct: There Was No Intent to Deceive the PTO

543. Mr. Lopez did not, at any time during all of his work related to the prosecution of the '473 patent, ever have an intent to deceive the PTO in any way. [T. Tr., Feb. 24, 2009 A.M. 63:22-25 (Lopez).]

544. There are at least "two perfectly valid reasons" why Mr. Lopez would not have attempted to deceive the PTO: (1) "it would be against the law and [Mr. Lopez is] an attorney and [he] wouldn't have done that" and (2) Mr. Lopez "wouldn't risk [his] license on the basis . . . [of] doing something as idiotic as attempting to deliberately hide a document." [T. Tr., Feb. 24, 2009 A.M. 63:22-64:15 (Lopez).]

1. No One Involved in the Prosecution of the '473 Patent Had Knowledge of the Young Papers During the Prosecution of the '473 Patent

545. Mr. Belley was not aware of Young '89 before or during the prosecution of the '473 patent. [Belley Dep. Tr. 139:5-12.] In fact, Mr. Belley never saw Young '89 before his deposition in this case. [Belley Dep. Tr. 26:3-10.]

546. Mr. Belley did not attend the Taipei conference. [Belley Dep. Tr. 27:10-13.]

547. Dr. Guay testified at his deposition that he was not involved in any discussions regarding a model hypothesizing how LTD_4 binds to a receptor. [Guay Dep. Tr. 67:19-23, 86:13-18, 102:9-14.]

548. Dr. Guay had never seen Young '89 before his deposition in this case. [Guay Dep. Tr. 83:5-11.]

549. Dr. Guay did not attend the Taipei conference. [Guay Dep. Tr. 81:10-15.]

550. Dr. Xiang had never seen the Young '89 model before preparing for his deposition in this case. [Xiang Dep. Tr. at 54:15-17.]

551. Dr. Leger does not recall having seen Young '89 before his deposition. [Leger Dep. Tr. 127:20-24.]

552. Dr. Leger did not attend the Taipei conference. [Leger Dep. Tr. 126:11-14.]

553. Patrick Roy did not see Young '89 before his deposition in this case. [Roy Dep. Tr. 48:16-20.]

554. Patrick Roy did not attend to the Taipei conference. [Roy Dep. Tr. 48:4-8.]

555. Dr. Zamboni did not see Young '89 any time before Dr. Zamboni's deposition in this case. [Zamboni Dep. Tr. 13:14-18, 14:6.]

556. Dr. Zamboni was not involved, substantively or otherwise, in the prosecution of the applications that led to the '473 patent. [Zamboni Dep. Tr. 29:6-9.]

557. Joseph Atkinson was the patent liaison for Merck at the time the '473 patent was prosecuted. [Atkinson Dep. Tr. 11:13-12:13; Zamboni Dep. Tr. 63:8-12.]

558. Dr. Atkinson had never seen Young '89 before he prepared for his deposition in this case. [Atkinson Dep. Tr. 61:23-62:1, 62:19-21.]

559. During the timeframe that Mr. Lopez was employed at Merck, there was a procedure in place by which materials that was proposed to be released to the public first had to be approved by certain individuals. [T. Tr., Feb. 24, 2009 A.M. 10:21-11:11 (Lopez).]

560. As part of this procedure, Mr. Lopez reviewed certain materials that were thought to be relevant to the subject matter of his patent prosecution docket. [*See* T. Tr., Feb. 24, 2009 A.M. 11:17-12:4 (Lopez).]

561. Mr. Lopez would review such documents so that he was sufficiently comfortable to release the information for publication, but he did not necessarily read every word of every publication. [*See, e.g.*, T. Tr., Feb. 24, 2009 A.M. 14:23-15:5; 19:14-22 (Lopez).]

562. Mr. Lopez testified that, when reviewing a proposed publication for publication disclosure, "If there had already been a publication or a patent application filed, then [he would have been] more likely to approve the document." [T. Tr., Feb. 24, 2009 A.M. 16:3-8.]

563. This is because, as Mr. Lopez understood such an indication on Form B of the manuscript review forms, there would have been nothing in the material that was not already covered by a pending patent application and/or that he should have been concerned about for some other reason. [T. Tr., Feb. 24, 2009 A.M. 16:3-18 (Lopez).]

564. Mr. Lopez's primary responsibility was to maintain a large patent prosecution docket that included all patents directed to respiratory indications, most of which originated from Merck Frosst. [T. Tr., Feb. 24, 2009 A.M. 7:11-20; 44:18-45:2 (Lopez).]

565. Because reviewing manuscripts for approval made up only a small part of Mr. Lopez's job responsibilities, he "couldn't give . . . an hour or two to reading each one" of the 100 or so manuscripts that he received each year. [T. Tr., Feb. 24, 2009 A.M. 60:7-15 (Lopez).] Therefore, Mr. Lopez sometimes read less of a proposed manuscript if there were indications that suggested to him that approval of the manuscript would not be problematic. *Id.*

566. Some of the factors that would influence the amount of time that Mr. Lopez devoted to certain manuscripts were whether the author, especially an author that Mr. Lopez trusted, indicated that there was nothing in the manuscript that had not been approved before; whether a patent had been issued regarding the subject matter of the manuscript; or whether a patent application had been filed regarding the subject matter of the manuscript. [T. Tr., Feb. 24, 2009 A.M. 60:16-61:3, 61:13-25 (Lopez).]

567. In light of the fact that Mr. Lopez did "probably 100 or more [manuscript approvals] on an annual basis and that this was a small part of [his] full docket of maybe 1200 or 2000 worldwide cases, [he] can't imagine that [he] would have had the time or the inclination to go back and check" every representation regarding whether particular manuscripts had been previously approved for publication. [T. Tr., Feb. 24, 2009 A.M. 71:19-72:8 (Lopez).]

568. Exhibit 1207 indicates that on November 9, 1987, Mr. Lopez approved for release an abstract relating to a proposed presentation that Dr. Young was scheduled to present in Toronto in the June 5th to June 11th, 1987 timeframe. [TEX 1207.0001.]

569. Exhibit 1207 also indicates that the relevant patent applications had already been filed covering the subject matter of this abstract. [TEX 1207.0003; T. Tr., Feb. 24, 2009 A.M. 15:12-16:2.]

570. According to the abstract, "Structure-activity relationships, special requirements for activity and the derivation of ***a*** refined model of the antagonist form of the LTD_4 receptor [were to] be presented. Application of these concepts to the design of a novel, highly potent and orally active LTD4 antagonist . . . [were to] be discussed." The abstract does not identify the model as the Young '89 model and does not further elaborate on the properties of the "refined model" mentioned above; nor does the abstract identify the source of the model to which it is referring. [TEX 1207.0004 (emphasis added).]

571. Exhibit 1411 indicates that on March 10, 1988, Mr. Lopez approved for release a manuscript of a proposed article written by Dr. Young, titled "The Development of New Anti-Leukotriene Drugs: L-648,051 and L-649,923, Specific LTD4 Antagonists." [TEX 1411.0001.]

572. Exhibit 1411 indicates that Mr. Lopez made a suggestion to delete certain language regarding clinical trials in this manuscript, but he does not now remember the exact context of the suggestion or how that language came to his attention. [T. Tr., Feb. 24, 2009 A.M. 17:12-19 (Lopez).]

573. At the end of the manuscript, several pages of unlabeled figures are attached. [TEX 1411.0030-36.]

574. Included in these figures is a depiction of a model of the LTD_4 receptor. [TEX 1411.0031.]

575. Mr. Lopez does not recall whether he had knowledge of the Young '89 model at the time he was reviewing the manuscript included in Exhibit 1411 or whether he specifically saw or paid attention to the depiction of the LTD_4 receptor model in the figures attached to the back of the manuscript. [T. Tr., Feb. 24, 2009 A.M. 19:20-20:12 (Lopez).]

576. Exhibit 1411 indicates that multiple patent applications had already been filed covering the subject matter of this manuscript. [TEX 1411.0002.]

577. Exhibit 1410 indicates that on April 25, 1988, Mr. Lopez approved for release a manuscript of what was eventually published as Young '89 in connection with Dr. Young's presentation at the Taipei conference. [TEX 1410.0001.] This occurred more than two years before the filing date of '887 application, the earliest continuation-in-part to which the '473 patent claims priority. [TEX 3001.]

578. Exhibit 1410 also indicates that although the "Comments" section of the manuscript review form states that "all of the material in this manuscript was previously cleared in 87-ms-1290," Mr. Lopez noted that this could not be the case because "1290 was an ***abstract*** only" (87-ms-1290 is the manuscript review form discussed above as Exhibit 1207). [TEX 1410.0001 (emphasis in original).]

579. Mr. Lopez does not recall the line of inquiry that led him to understand that all of the material in the manuscript included in Exhibit 1410 could not have been cleared in the previous publication. [T. Tr., Feb. 24, 2009 A.M. 70:11-71:18 (Lopez).]

580. Exhibit 1410 also indicates that multiple patent applications already had been filed covering the subject matter of this manuscript. [TEX 1410.0002.]

581. Regarding the Young '89 model as presented in the manuscript that Mr. Lopez approved for publication on April 25, 1988, "[o]ther than it appears on this page of this manuscript that [he] apparently reviewed, then [he] must have seen it. Whether [he] studied it or read it in detail, [he does]n't remember." [T. Tr., Feb. 24, 2009 A.M. 27:6-12 (Lopez).]

582. Exhibit 1285 indicates that on August 25, 1988, Mr. Lopez approved for release a manuscript of a proposed article written by Dr. Zamboni and others, titled "The Development of L-660,711, A Potent Orally Active LTD_4 Antagonist." [TEX 1282.0001.]

583. Exhibit 1285 also indicates that multiple patent applications had already been filed covering the subject matter of this manuscript. [TEX 1285.0003.]

584. At the top of the fourth page of the submitted manuscript, the proposed article states that the Merck scientists "recently described ***a*** hypothetical model for the LTD_4 receptor containing 3 binding zones: a flat lipophilic (triene) binding site, one polar and one ionic site." [TEX 1285.0007 (emphasis added).] The proposed article mentions that L-660,711 "represents the type of structure predicted to be required for potent activity by our receptor model" but does not identify the model as the Young '89 model and does not further elaborate on the properties of the hypothetical model; nor does the proposed article identify the Young '88 or Young '89 articles as the source of the model to which it is referring. [*Id.* at 0009.]

585. Exhibit 104 indicates that on October 25, 1988, Mr. Lopez approved for presentation at the Leukotrienes and Prostanoids International Conference in Israel an article written by Dr. Young and others, titled "L-660,711, A Potent Selective and Orally Active Antagonist of LTD4." [TEX 0104.0012.] Exhibit 104 contains both a published version of the article and a proposed manuscript; it is unclear which version Mr. Lopez reviewed. [*See generally id.* at 0001-5, 0015-21; T. Tr., Feb. 24, 2009 A.M. 30:1-32:4 (Lopez).]

586. Exhibit 104 indicates that the relevant patent applications already had been filed covering the subject matter of this manuscript and that the manuscript had been previously approved for publication. [TEX 0104.0009-11.]

587. At the top of the third page of the submitted manuscript, the proposed article states that "[t]he evolution of the initial lead . . . to optimize lipophilic, polar, and ionic binding in keeping with ***a*** model we have developed for the LTD_4 receptor led to the identification of L-660,711." [TEX 0104.0017 (emphasis added); *see also* T. Tr., Feb. 24, 2009 A.M. at 31:20-32:4 (Lopez).] The manuscript of the proposed article does not identify the model as the Young '89 model in its text and does not further elaborate on the properties of the model. The manuscript does cite Young '88 in a footnote referencing the model [TEX 0104.0021], but there is no indication in the trial record that Mr. Lopez saw or paid particular attention to any of the footnotes, much less the one referencing Young '88.

588. Exhibit 105 indicates that on November 1, 1989, Mr. Lopez approved for release a manuscript of a proposed article written by J.Y. Gauthier and others, titled "3-((((3-(2-(7-Chloroquinolin-2-yl)-(E)-ethenyl)phenyl)-3-dimethylamino-3-oxopropylthio)methyl)propionic Acid (L-660,711) [MK-571]: Stereospecific Synthesis, Assignment of Absolute Configuration and Biological Activity of the Enantiomers." [TEX 0105.0014.]

589. Exhibit 105 also indicates that U.S. Patent No. 4,851,409, which was disclosed to the PTO during the prosecution of the '473 patent, had already been issued covering the subject matter of this manuscript. [TEX 0105.0012.]

590. At the top of the second page of the submitted manuscript, the proposed article states that "[t]he development of [L-660,711] evolved closely with our better understanding and refinement of ***a*** model of a LTD4 receptor based on analysis of biological data available in the literature on leukotriene analogues and antagonists. In keeping with this model, [L-660,711] embodies a planar lipophilic backbone with extended conjugation, coupled to two polar chains, one ionizable the other not." [TEX 0105.0016 (emphasis added).] The manuscript of the proposed article does not identify the model as the Young '89 model in its text and does not further elaborate on the properties of the model. The manuscript does cite Young '88 in a footnote referencing the model [TEX 0105.0016], but there is no indication in the trial record that Mr. Lopez saw or paid particular attention to any of the footnotes, much less the one referencing Young '88.

591. Exhibit 1467 indicates that on January 1, 1990, Mr. Lopez approved for release an abstract regarding a scheduled presentation by Dr. Young at a conference later that year. [TEX 1467.0010-11.]

592. The actual abstract is not included in Exhibit 1467. [*See* T. Tr., Feb. 24, 2009 A.M. at 34:2-9 (Lopez).] A copy of what may have been the abstract states that "with the aid of computer modeling and the application of analysis of structure activity relationships, a hypothetical model of the LTD4 receptor has been evolved." [TEX 1467.0010.] The supposed abstract does not identify the model as the Young '89 model and does not further elaborate on the properties of the model; nor does the proposed article identify the source of the model to which it is referring.

593. Exhibit 1263 indicates that on August 19, 1990, Mr. Lopez approved for release a manuscript of a proposed article written by Dr. Anthony Ford-Hutchinson and others, titled "Leukotriene Blockers, Novel Therapeutic Strategies for the Treatment of Asthma." [TEX 1263.0001.]

594. Exhibit 1263 also indicates that multiple patent applications had already been filed regarding this subject matter and that U.S. Patent No. 4,851,409, which was disclosed to the PTO during the prosecution of the '473 patent, had already been issued covering the subject matter of this manuscript. [TEX 1263.0003.] Exhibit 1263 also indicates that this manuscript had been previously cleared for publication. [TEX 1263.0002.]

595. At the top of the fifth page of the submitted manuscript, "***a*** hypothetical receptor model" is discussed. [TEX 1263.0008 (emphasis added).] The manuscript goes on to explain that "[r]ecent studies with LTD_4 antagonists, and in particular with the enantiomers of MK-0571, have allowed us ***to propose*** the following conceptual model of the LTD_4 receptor." *Id.* (emphasis added). The proposed model lists five distinct properties, several of which are not present and not alleged by Teva to be present in the Young '89 model. *Id.* The proposed article does not identify the model as the Young '89 model or as an evolution of the Young '89 model, nor does the proposed article cite to Young '88 or Young '89 as providing inspiration for the described model.

596. At the end of the manuscript, several pages of unlabeled figures are attached. [TEX 1263.0020-24.] There is no indication in the trial record that Mr. Lopez specifically saw or paid attention to the unlabelled figures at the back of the manuscript.

597. Exhibit 1465 indicates that on March 22, 1991, Mr. Lopez approved for release a manuscript of a proposed article written by Dr. Young and others, titled "Conformational Analysis of Leukotrienes and Related Compounds for Mapping the LTD4 Receptor: Application to the Design of Novel Anti-Asthma Drugs." [TEX 1465.0018.]

598. Exhibit 1465 indicates that the subject matter of this submission had already been approved for release four times. [TEX 1465.0016; T. Tr., Feb. 24, 2009 A.M. 38:17-24 (Lopez).]

599. Mr. Lopez testified that the manuscript of the proposed article in Exhibit 1465 "is the kind of document that [he] would probably have given very little review to since the author has already said that there's nothing in here that hasn't already been – not published, but approved for publication. So my level of reading would have been minimal, I suspect." [T. Tr., Feb. 24, 2009 A.M. 39:21-40:3.]

600. Exhibit 1227 indicates that on April 1, 1992, Mr. Lopez approved for release a manuscript of a proposed article written by Dr. Zamboni and others, titled "Development of a Novel Series of Stryrl Quinoline Compounds as High Affinity LTD4 Receptor Antagonists: Synthetic and Structural Activity Studies Leading to the Discovery of (3-(3-(2-(7-Chloro-2-Quinolinyl)-(E)-Ethenyl)Phenyl))-3-Dimethylamino-3-Oxopropylthio)Methyl)Thio)Propionic Acid) (MK-571)." [TEX 1227.0001.]

601. At the top of the second page of the submitted manuscript, the proposed article states that the Merck scientists "derived and recently described ***a*** hypothetical model for the LTD_4 receptor comprising three major binding units: A flat lipophilic (triene) binding site, a hydrophobic (polar) binding site and a hydrophilic (ionic) binding site which recognizes one of the carboxylate groups of LTD_4." [TEX 1227.0006 (emphasis added).] The manuscript of the proposed article does not identify the model as the Young '89 model in its text and does not further elaborate on the properties of the model. [*Id.*] The manuscript does cite Young '89 in a footnote referencing the model [*id.*], but there is no indication in the trial record that Mr. Lopez saw or paid particular attention to any of the footnotes, much less the one referencing Young '89.

602. Exhibit 1227 indicates that two patents had already been issued regarding the subject matter of the manuscript, U.S. Patent No. 4,961,203 and 4,851,409, both of which were disclosed to the PTO during the prosecution of the '473 patent. [TEX 1227.0003.]

603. Mr. Lopez does not know whether the manuscripts of articles proposed for submission to journals or other publications were ever submitted, accepted, and/or published in those journals. [*See* T. Tr., Feb. 24, 2009 A.M. 36:9-12 (Lopez).]

604. Teva's Interrogatory No. 6 requested that Merck:

> "Identify each person involved in the prosecution of the Patent-in-Suit who, prior to October 15, 1996, received, reviewed, or had knowledge of either of the following two references: Robert Young, Structural Analysis of Sulfido-Peptide Leukotrienes: Application to the Design of Potent and Specific Antagonists of LTD4, 19 Advances in

> Prostaglandin, Thomboxane, and Leukotriene Research 643, 643-646 (1989); and Robert Young, The Development of New Anti-Leukotriene Drugs, 13 Drugs of the Future 745, 745-759 (1988)."
>
> [TEX 0212.0009.]

605. This Interrogatory specifically refers to the Young '89 and Young '88 references as they were published in Advances in Prostaglandin, Thomboxane, and Leukotriene Research, and Drugs of the Future, respectively. [TEX 0212.0009.]

606. Because Teva's Interrogatory No. 6 was restricted to knowledge of the Young '88 and Young '89 references as published, Mr. Lopez's review of a draft manuscript that he released for potential publication is not responsive to Interrogatory No. 6.

607. Merck has always maintained and continues to maintain this position.

608. There is no evidence that Mr. Lopez received or reviewed published versions of any of the draft manuscripts discussed at trial, including Young '88 or Young '89.

609. In fact, Mr. Lopez "[does]n't know that [Young '89] actually ever published." [T. Tr., Feb. 24, 2009 A.M. 58:7 (Lopez).]

610. There is no evidence that anyone involved in the prosecution of the '473 patent had knowledge of the published versions of Young '88 or Young '89.

611. Mr. Lopez reviewed a manuscript of Young '89 before October 15, 1996, but he did not review the Young '89 reference as defined in Teva's Interrogatory No. 6. [*See* T. Tr., Feb. 24, 2009 A.M. 21:25-22:20.]

2. Gabriel Lopez Does Not Recall Considering Young '89

612. The prosecution of the patents to which the '473 patent claims priority represents only one of the "maybe 1,000 or 2,000 cases" for which Mr. Lopez was responsible. [T. Tr., Feb. 24, 2009 A.M. 44:20-25 (Lopez).]

613. In the 1990 through 1993 timeframe, Mr. Lopez would have had a general understanding that the Merck scientists would try to understand how to construct a receptor antagonist through the use of models and that receptors typically have three or more points of contact. [T. Tr., Feb. 24, 2009 A.M. 42:23-43:2; 43:23-44:13 (Lopez).] But Mr. Lopez does not recall being aware of the specific receptor model disclosed in Young '89.

614. Mr. Lopez did approve for release a manuscript of what was eventually published as Young '89, but that occurred more than two years before the filing date of '887 application, the earliest continuation-in-part to which the '473 patent claims priority. [FF 483.] The manuscript that Mr. Lopez approved was also only four pages long. [TEX 1410.]

615. Failure to recall specific details about work conducted years ago does not amount to evidence of intent to deceive. [*See, e.g.* Goshko Dep. Tr. 157:13-158:10.] Mr. Marc Goshko, Teva's executive director of legal affairs, agreed that the fact that he did not recall whether he had reviewed Young '89 just one year earlier was not indicative of an intent to deceive. [*Id.*]

616. Mr. Lopez does not have any recollection of ever considering whether or not to disclose Young '89 to the PTO during the prosecution of the '473 patent or of making a conscious decision to do so or not to do so. [T. Tr., Feb. 24, 2009 A.M. 60:1-6 (Lopez).]

E. Gabriel Lopez Satisfied His Duty of Candor

617. Mr. Lopez had an understanding in the 1990 through 1993 timeframe that he had an obligation to disclose information to the PTO that was material to the patentability of pending claims. [T. Tr., Feb. 24, 2009 A.M. 52:4-9 (Lopez).]

618. Mr. Lopez testified that an Information Disclosure Statement ("IDS") is "a mechanism used to comply with the duty of disclosure and the IDS . . . is a method of presenting to the examiner documents that are viewed as something the examiner might want to see." [T. Tr., Feb. 24, 2009 A.M. 62:15-22.]

619. During the prosecution of the '473 patent, Mr. Lopez complied with his duty of candor by disclosing several references to patents listing Dr. Young as an inventor. [*See* T. Tr., Feb. 24, 2009 A.M. 62:23-63:21 (Lopez); *see also* TEX 1442.0130 (disclosing several patents, including U.S. Patent No. 4,962,203 to Young), 0134 (disclosing two patents, including European Patent Application 0 318 093 to Young); TEX 1444.0179 (disclosing several patents, including U.S. Patent No. 4,962,203 and European Patent Application 0 318 093, both to Young), 0303 (disclosing several patents in an International Search Report Form, including U.S. Patent No. 4,661,499 and European Patent Application 0 206 751, both to Young), 0305 (disclosing several patents, including U.S. Patent No. 4,851,409, European Patent Application 0 399 818, European Patent Application 0 271 287, European Patent Application 0 233 763, and European Patent Application 0 206 751; all to Young).]

620. Given that Mr. Lopez disclosed so many materials published by Dr. Young, there is no reason to believe that he would try and hide a document which is easily discoverable later. [*See* T. Tr., Feb. 24, 2009 A.M. 64:8-11 (Lopez).]

Dated: March 18, 2009

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